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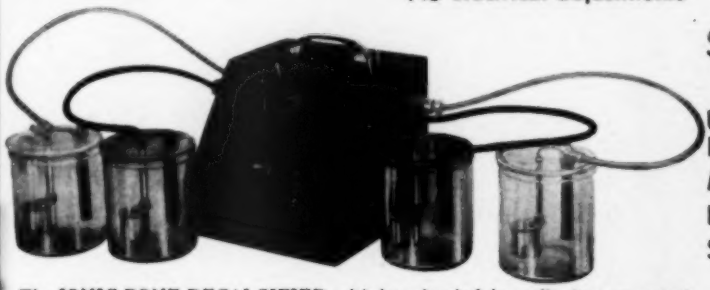

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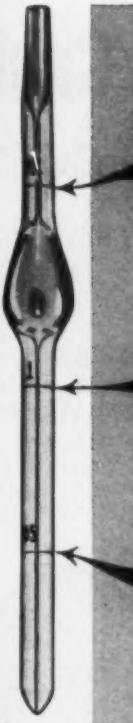

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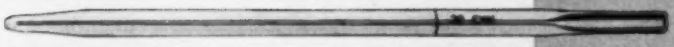

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A HISTOLOGICAL STUDY OF THE HEART LESIONS IN POTASSIUM-DEFICIENT RATS

JOHN E. FRENCH, M.D.
CHICAGO

THE LESIONS produced in the myocardium of weanling rats by diets deficient in potassium have now been described by a number of authors.[1] In recent studies Cannon and his associates have shown that severe lesions of a similar nature, resulting in myocardial failure within a short time, may be produced in protein-depleted adult rats by feeding them a repletion diet deficient in potassium. These lesions are produced readily and appear to be more extensive in character than those previously described.[2] Consequently, such animals provide very suitable material for a histological study of the development and morphologic aspects of the cardiac lesion in potassium deficiency and the changes which the involved tissue undergoes when potassium is restored to the diet.

MATERIALS AND METHODS

Twenty-two male albino rats of the Sprague-Dawley strain (initial weight, 200 to 230 gm.) were subjected to slow protein depletion until they showed a 30 to 40% weight loss. They were then given a repletion ration which had an adequate content of all essential food factors but in which all potassium had been replaced by sodium in the salt mixture (for details see Cannon, Frazier, and Hughes [2]). Half the animals were maintained on this regimen for periods of 14 to 20 days and then were killed. The heart lesions in this group of animals, which was potassium-deficient throughout, will be described as the progressive type.

The remaining animals were maintained on the potassium-deficient diet for periods of 12 to 18 days and then given a daily supplement of 200 mg. of potassium chloride for various periods of 2 to 10 days before being killed. The lesions observed in this group of animals, receiving potassium at the time of death, will be described as the regressive type. In addition, two groups of control animals were studied: protein-depleted rats which had not received any form of repletion diet, and depleted animals which had received the repletion diet with an adequate supplement of potassium throughout.

Dr. French is Rockefeller Foundation Traveling Fellow.

From the Departments of Medicine and Pathology, University of Chicago.

1. (*a*) Schrader, G. A.; Prickett, C. O., and Salmon, W. D.: Symptomatology and Pathology of Potassium and Magnesium Deficiencies in the Rat, J. Nutrition **14**:85-109, 1937. (*b*) Thomas, R. M.; Mylon, E., and Winternitz, M. C.: Myocardial Lesions Resulting from Dietary Deficiency, Yale J. Biol. & Med. **12**:345-360, 1940. (*c*) Follis, R. H.; Orent-Keiles, E., and McCollum, E. V.: The Production of Cardiac and Renal Lesions in Rats by a Diet Extremely Deficient in Potassium, Am. J. Path. **18**:29-39, 1942. (*d*) Kornberg, A., and Endicott, K. M.: Potassium Deficiency in the Rat, Am. J. Physiol. **145**:291-298, 1946. (*e*) Smith, S. G.; Black-Schaffer, B., and Lasater, T. E.: Potassium Deficiency Syndrome in the Rat and the Dog, Arch. Path. **49**:185-199, 1950.

2. Cannon, P. R.; Frazier, L. E., and Hughes, R. H.: Influence of Potassium on Tissue Protein Synthesis, Metabolism **1**:49-57, 1952.

The animals were killed with ether, and the entire heart was taken for histological examination. Blocks, either transverse or longitudinal, were taken through the entire heart, and fixed in formal-sublimate, neutral formalin, and chilled acetone. Various staining techniques were carried out, but the ones found to be most informative in studying cardiac muscle were the Gomori modification of the trichrome method [3] and the periodic acid-Schiff (P.A.S.) method of McManus,[4] using the formol-sublimate-fixed tissues. Acetone-fixed tissues were stained for acid and alkaline phosphatase and for esterases, using Gomori's methods.[5] Frozen sections were prepared from the formalin-fixed material and stained for lipids with Sudan III and Sudan black B. Attempts to demonstrate potassium by the sodium cobaltonitrite method in frozen-dried tissues did not give satisfactory results.

RESULTS

Progressive Lesions.—Microscopic evidence of myocardial lesions was found in all animals that had been subjected to potassium deficiency but was absent in controls. The extent of the lesions varied in different animals but was usually more severe when potassium deficiency had been more prolonged. Lesions were particularly widespread in two animals which died after 14 and 18 days on the potassium-deficient regimen.

The distribution of the myocardial lesions was characteristic. The earliest changes occurred just beneath the ventricular endocardium and affected small groups of fibers in the columnae corneae and the papillary muscles. Later the lesions became massive, involving large areas in the inner half of the ventricular wall. They often showed a fairly sharply defined border. The two ventricles were affected about equally, although the inner half of the lateral wall of the right ventricle was apparently prone to severe lesions (Fig. 1). In addition to the larger, well-defined lesions, small focal changes, involving only a few muscle segments, were scattered throughout the myocardium, extending as far as the epicardial surface. Changes were less pronounced in the atrial myocardium, but in association with the more severe ventricular lesions there were diffuse degenerative changes in the muscle, interstitial edema, and round cell infiltration. No changes were seen in the valves.

The essential histological feature of the progressive lesions was a primary degeneration of muscle substance, which progressed through the stage of necrobiosis to complete disintegration of some muscle fibers. In the early stages of this change groups of fibers showed loss of striation and homogeneous staining with the red component of the trichrome stain. Some fibers, viewed longitudinally, showed transversely arranged bands of this red-staining hyaline material which appeared to be formed by clumping of the myofibrils. In the more advanced stages of degeneration the hyaline material disintegrated, forming irregular clumps and granules, still confined within an apparently intact connective tissue sheath (Fig. 2). Along with these changes, the muscle nuclei underwent degeneration, appearing pyknotic at the stage of hyaline change and disappearing at the time of the disintegration of the fiber.

---

3. Gomori, G.: A Rapid One-Step Trichrome Stain, Am. J. Clin. Path. **20**:661-664, 1950.

4. McManus, J. F. A.: The Periodic Acid Routine Applied to the Kidney, Am. J. Path. **24**:643-654, 1948.

5. Gomori, G.: (*a*) Alkaline Phosphatase of Cell Nuclei, J. Lab. & Clin. Med. **37**:526-531, 1951; (*b*) The Histochemistry of Esterases, in International Review of Cytology, edited by G. H. Bourne and J. F. Danielli, 1952, Vol. 1, pp. 323-335; (*c*) An Improved Histochemical Technique for Acid Phosphatase, Stain Technol. **25**:81-85, 1950.

Although this was the most conspicuous type of change in the muscle, other fibers, either within or on the edge of the lesions, showed evidence of less severe injury and were apparently still viable. Some fibers were swollen, pale-staining, or vacuolated and had large vesiculated nuclei, in which the nucleoli were unusually prominent. Others were shrunken and stained poorly with the trichrome stain, but still retained large vesicular nuclei. In occasional fibers this vesiculation of the nucleus was exaggerated, so that the nucleolus appeared to be suspended by threads in a large nuclear vacuole. A few muscle nuclei were surrounded only by a rim of

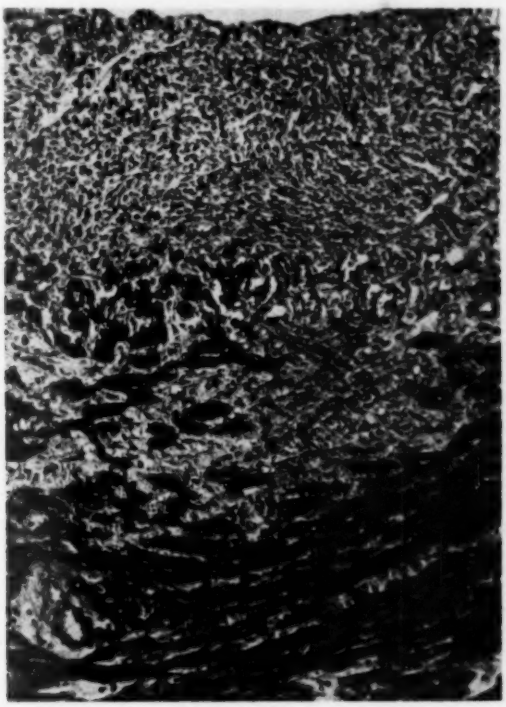

Fig. 1.—An extensive lesion involving the inner third of the lateral wall of the right ventricle in an animal that had been without potassium for 22 days. In addition to the massive lesion there are small focal changes in the underlying muscle.

sarcoplasm and formed apparently isolated cells of muscle origin such as have been often described in degenerating striated muscle as myogenous cells.[6] These cells, however, were rare, and there was no evidence that they contributed largely to the collections of round cells at the site of the lesions.

6. Smith, A. J.: On the Histological Behavior of Cardiac Muscle in 2 Examples of Organization of Myocardial Infarct, Univ. Penn. M. Bull. **17**:227-234, 1904. Gouley, B. A.; McMillan, T. H., and Bellet, S.: Idiopathic Myocardial Degeneration Associated with Pregnancy, Especially Puerperium, Am. J. M. Sc. **194**:185-199, 1937.

The other staining techniques used showed some further changes in the degenerating muscle. In occasional fibers there was an accumulation of fine fatty droplets or increased staining with Sudan black B which could not be resolved into droplets. The extent of this fatty change varied considerably in different animals. It usually involved only a few fibers near the edge of the lesions, but in one animal (potassium-deficient for 20 days) nearly the whole of the inner third of the myocardium was affected. It should be emphasized that no fatty change was found in the myocardium of protein-depleted control animals.

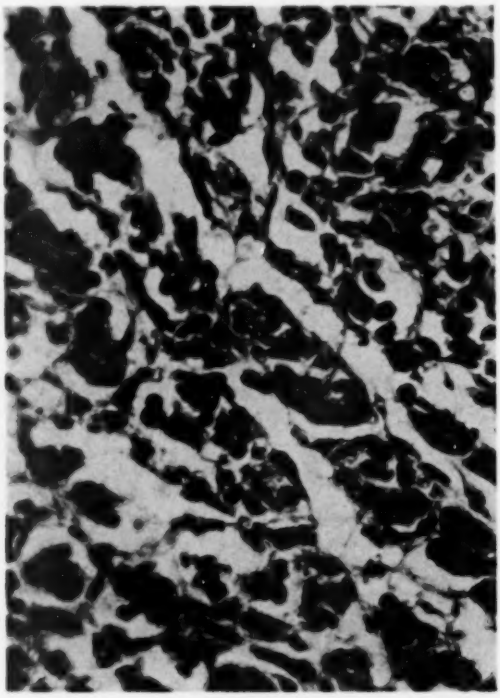

Fig. 2.—A lesion of the left ventricle in an animal deprived of potassium for 18 days. Many of the muscle fibers are fragmented or have disappeared. Collections of macrophages are seen within the fiber sheath. A few shrunken fibers have survived within the lesion. Trichrome stain; × 570.

Degenerate fibers had an increased affinity for the basic dyes toluidine blue and pyronine and, in both acetone- and formalin-fixed, paraffin-embedded material, stained red with the periodic acid-Schiff technique (Fig. 3). In the normal rat heart, only glycogen and the interstitial connective tissue stain red with this method, and the significance of the positive periodic acid-Schiff reaction of degenerating myocardial fibers is not entirely clear. The color persisted after treatment with saliva or 1% malt diastase in phosphate buffer and was therefore not due to glycogen. Certain phospholipids and unsaturated fats stain with the periodic acid-

Schiff technique [7] and may be relatively insoluble in fat solvents after fixation. A fatty change in the degenerate muscle appeared to be associated with the positive staining, since the same fibers had an increased affinity for Sudan black B even in formalin-fixed, paraffin-embedded material, and the extent of the change corresponded closely with the distribution of lipid as seen in frozen sections stained with Sudan black B. On the other hand, a direct staining with Schiff's reagent, indicative of preformed fatty aldehydes, was not obtained, and it was not possible to effect complete extraction of the material stained, either with methanol-chloroform or

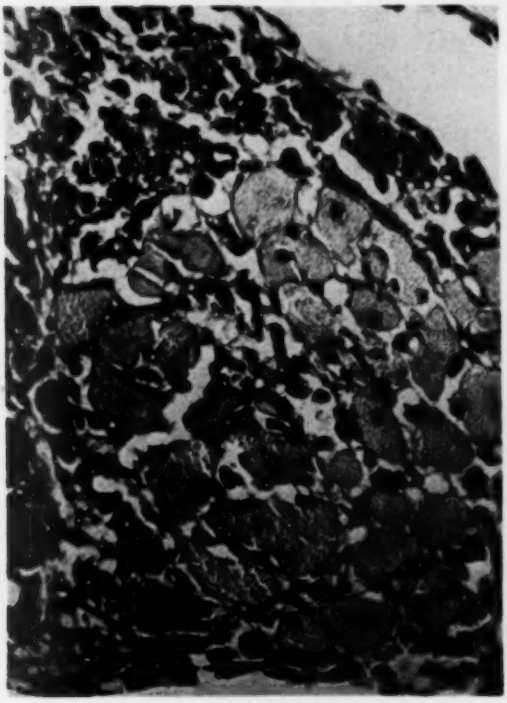

Fig. 3.—Periodic acid-Schiff-hematoxylin stain of a lesion in the right ventricle after 16 days of potassium deficiency. The periodic acid-Schiff stain is taken by granular muscle debris and by some fibers around the edge of the lesion which have lost their fibrillar pattern. × 480.

pyridine at 60 C, even from acetone-fixed sections. The possibility that an insoluble polysaccharide or glycoprotein plays a role in the reaction must therefore be considered. A mucoid type of degeneration occurring in human cardiac muscle has recently been described.[8]

7. Wolman, M.: Staining of Lipids by the Periodic-Acid-Schiff Reaction, Proc. Soc. Exper. Biol. & Med. **75**:583-585, 1950.

8. Spencer, H.: Mucoid Degeneration of the Heart Muscle, J. Path. & Bact. **62**:653-654, 1950.

The acid phosphatase technique gave no reaction in the normal rat heart but showed quite notable activity in the lesions. Localization was not sharp, but there appeared to be activity both in degenerating fibers and in the surrounding inflammatory cells. The reaction was abolished by pretreatment of the slide with strong iodine solution U. S. P. or by adding fluoride to the incubating mixture and was not therefore due to nonspecific adsorption of lead phosphate by necrotic tissue.

Associated with these changes in the muscle fibers there was a well-marked interstitial reaction. This was seen in relation to the earliest stage of fiber degenera-

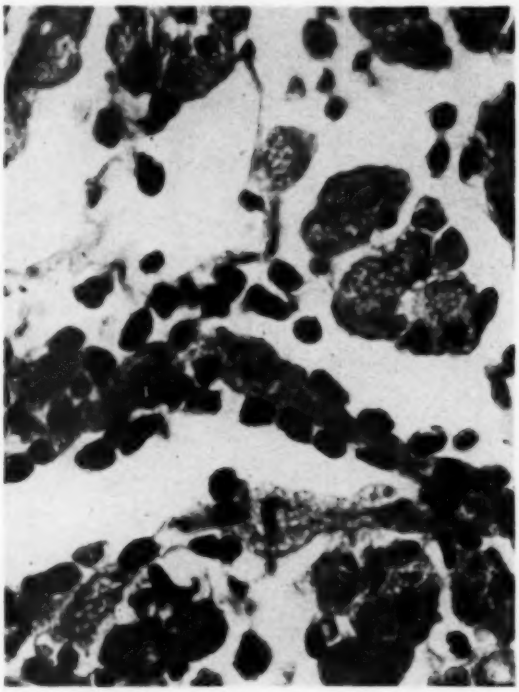

Fig. 4.—Early degenerative changes in the right ventricle of an animal which had been potassium-deficient for 14 days. The central fiber has lost its striation and is beginning to show fragmentation. Around it there is widening of the interstitial space and accumulation of polyblasts. Trichrome stain; × 950.

tion as a widening of the interstitial space, enlargement and multiplication of fixed connective tissue cells, fibroblasts, and endothelial cells, and increased staining of connective tissue fibrils. In addition cells of the polyblast and macrophage class collected at the site of the lesion. In the early stages of degeneration these cells were alined along the borders of the damaged fibers (Fig. 4), and later, as the fiber material disintegrated, they appeared within the connective tissue sheath surrounding the muscle detritus. The activity of these cells resulted in removal, by phagocytosis, of the dead muscle, so that the center of the more advanced lesions

consisted of a rather loose reticular tissue from which all evidence of the degenerated fibers had disappeared. Overlying the lesions in the endocardial surface, the endothelial cells had a cuboidal shape and appeared crowded together. This change was not associated with thrombus formation in the ventricles, but an atrial thrombus was seen in one animal.

Apart from these morphological changes in the interstitial tissue, shown most clearly in the trichrome stains, some additional changes were observed with the other methods used. In the early stages of the interstitial reaction there was an

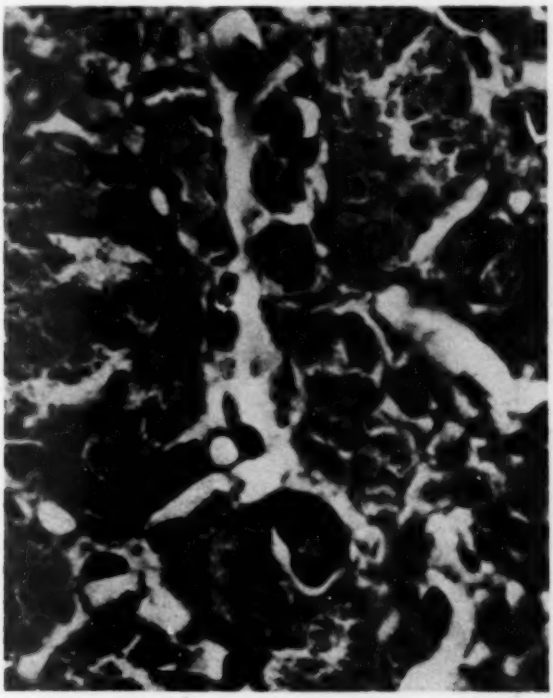

Fig. 5.—The edge of a lesion in the right ventricle in an animal which had been without potassium for 12 days and was then given potassium for 8 days. A group of small muscle fasciculi is seen among connective tissue elements at the center. Other fibers are swollen and show irregularity of staining and distribution of the myofibrils. Trichrome stain; × 1,230.

increased stainability of connective tissue fibrils with the periodic acid-Schiff technique. Many of the phagocytic cells contained granules of periodic acid-Schiff staining material which was not removed by diastase or chloroform-methanol extraction. Alkaline phosphatase activity was confined to the capillary endothelium and showed clearly the extension of capillaries among the degenerating fibers. The α-naphthol esterase technique, which stains certain fixed connective tissue cells in the rat heart,[5b] showed these cells also in the lesions, though not increased in number

except just beneath the endocardium. The esterase A. S. technique [5] stained the cytoplasm of the macrophages, and may be of value in identifying these cells in the rat.

In conclusion the interstitial reaction always appeared to be secondary to the degeneration of muscle fibers. It resulted in rapid removal of muscle debris, leaving an empty connective tissue framework in which there was only a moderate increase of fixed connective tissue cells.

Regressive Lesions.—After a given period of potassium deficiency the lesions in this group were much less conspicuous than those in the preceding group. The

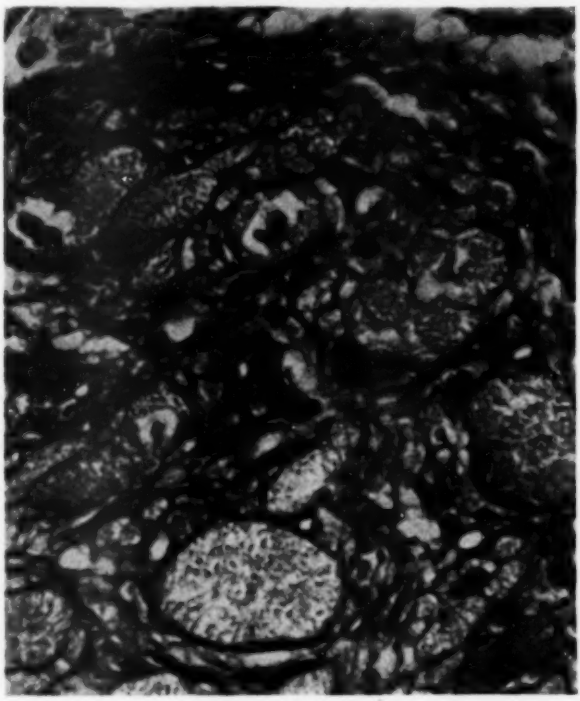

Fig. 6.—Lesion from an animal receiving the potassium supplement for 10 days after being deficient for 12 days. The cellular reaction has cleared. Connective tissue fibrils are thickened and condensed. The surviving muscle shows irregular fasciculation. Periodic acid-Schiff-hematoxylin; × 940.

lesions could be identified, however, in all the animals and had the same general distribution. The histological appearances indicated that the change in the lesions was due to an arrest of the degenerative process, compensatory changes in surviving muscle fibers and subsidence of the interstitial reaction.

After potassium had been restored to the diet for two days, there were occasional fibers which showed the hyaline type of degeneration and stained pink with the periodic acid-Schiff technique, but thereafter no such fibers could be identified in any of the regressive lesions. Granular muscle detritus was seen in and around

macrophages up to the third day, but not later than this. With the removal of the muscle debris, the cellular exudate cleared, leaving a loose connective tissue which in places appeared condensed or collapsed, but did not show evidence of continued fibroblastic proliferation. A few macrophages containing periodic acid-Schiff staining granules persisted at the 10th day.

Muscle fibers which had survived the degenerative process showed changes which were interpreted as indicating recovery and hypertrophy but no conclusive evidence of new fiber formation. Fibers in or around the lesions on the third day of potassium repletion appeared swollen, stained poorly with the trichrome stain, and had large nuclei, often with multiple nucleoli. Enlarged, elongated nuclei occurred particularly near the free ends of broken fibers, where they were often arranged end to end in pairs. Over the 10-day period of potassium repletion, however, no mitotic figures were observed in muscle, nor any multinucleate sarcoplasmic masses such as are seen in regenerating skeletal muscle.

A conspicuous feature of the muscle within or near the lesions was the irregularity of its fascicular pattern. Where fibers were cut transversely, they showed variation in size and, in places, irregular distribution of myofibrils within the sarcoplasm. Small fasciculi, containing only two or three myofibrils, could be identified among the connective tissue elements, and larger bundles, which had the outline of a single hypertrophied muscle fiber, could be seen with the periodic acid-Schiff technique to be divided by fine septa into a number of irregular-sized fasciculi. In some of these fasciculi the myofibrils had a peripheral arrangement in the sarcoplasm (Figs. 5 and 6). The ends of broken fibers, where viewed longitudinally, showed tapering, feebly striated tips, or, more commonly, the myofibrils appeared to be splayed out among the surrounding connective tissue elements. Up to the 10th day, however, there was no evidence of newly formed sarcoplasmic buds growing out into the connective tissue spaces or of new fibers being formed from any myogenous cells which might have persisted within the lesions. At this stage, the sheath of degenerated muscle which had shown quite clearly in the progressive lesions was collapsed so that the ends of broken fibers appeared to be sealed off by connective tissue. The acid phosphatase activity was much less pronounced in the regressive lesions but persisted in a few cells up to the 10th day. The cells staining with the α-naphthol esterase technique were increased in number apparently as a result of connective tissue condensation.

COMMENT

The progressive lesions in these animals appear to be identical with those in weanling rats fed a potassium-deficient diet, described first by Schrader, Prickett and Salmon,[1a] and subsequently by Thomas, Mylon and Winternitz,[1b] and Follis, Orent-Keiles, and McCollum.[1c] Histological accounts, based on staining with hematoxylin and eosin, left some doubt as to the nature of the changes in the myocardium. Peschel, Black-Schaffer, and Schlayer [9] have made a more detailed study of the heart lesions in potassium-deficient rats given desoxycorticosterone with or without high sodium intake. Using the Mallory trichrome stain, they stressed the primary nature of the muscle degeneration.

9. Peschel, E.; Black-Schaffer, B., and Schlayer, C.: Potassium Deficiency as Cause of the So-Called Rheumatic Heart Lesions of the Adaption Syndrome, Endocrinology **48**:399-407, 1951.

The present findings confirm this view that the essential feature of the cardiac lesion in potassium deficiency is a degeneration of muscle substance which progresses through the stage of necrobiosis to complete disintegration of some fibers. Morphologically, this process is in no way specific for potassium deficiency. It is analogous to the changes in skeletal muscle in Zenker's degeneration [10] and in cardiac muscle in diphtheria.[11] Similar appearances of fiber degeneration have been observed both in skeletal and in cardiac muscle following injury of many kinds.[12] The apparent predilection of the lesion for the papillary muscles is also seen in other types of primary parenchymatous lesions.[13]

Any attempt to explain how potassium deficiency brings about this degeneration of muscle can, on present evidence, be only speculative. It is clear that the usual concept of toxic action as the cause of necrosis must be broadened to include the effect of a deficiency, or more probably an imbalance, of normal cell constituents. It is known from the work of the school of Szent-Györgyi that the physical state of the actomyosin complex in muscle is highly dependent on the presence and relative concentrations of the alkali and alkaline earth metals.[14] It seems not improbable, therefore, that an intracellular ionic imbalance might bring about clumping and retraction of contractile material such as that observed by Spiedel [12] in injured living muscle. On the other hand, the biochemical lesion may involve primarily the energy-producing mechanism; it is known, for example, that potassium ions are required for the reaction phosphopyruvate + adenosine diphosphate pyruvate + adenosine triphosphate.[15] In any event, it is unlikely that the lesion will have a simple explanation in terms of potassium deficiency, since the severity has been shown to be influenced greatly by sodium intake,[16] acid-base balance,[17] and the adrenocortical hormones.[18] It seems probable that cardiac muscle is susceptible to injury from an intracellular ionic imbalance which can be brought about in a number of ways.

The interstitial reaction in the progressive lesions, consisting of local edema, mobilization of macrophages, and some proliferation of fibroblasts and capillary endothelium, is secondary to the degeneration of muscle fibers. There are thickening

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12. Spiedel, C. C.: Studies of Living Muscle: Growth, Injury and Repair of Striated Muscle as Revealed by Prolonged Observations of Individual Fibers in Living Frog Tadpoles, Am. J. Anat. **62**:179-236, 1938; Histological Changes in Single Fibers of Striated Muscle During Contraction and Clotting, ibid. **65**:471-529, 1939.

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16. Meyer, J. H.; Grunert, R. R.; Zepplin, M. T.; Grummer, R. H.; Bohstedt, G., and Phillips, P. H.: Effect of Dietary Levels of Sodium and Potassium on Growth and on Concentrations in Blood Plasma and Tissues of White Rat, Am. J. Physiol. **162**:182-188, 1950.

17. Darrow, D. C.; Schwartz, R.; Ianucci, J. F., and Coville, F.: The Relation of Serum Bicarbonate Concentration to Muscle Composition, J. Clin. Invest. **27**:198-208, 1948.

18. Darrow, D. C.: Effect of Low Potassium Diet and Desoxycorticosterone on the Rat Heart, Proc. Soc. Exper. Biol. & Med. **55**:13-14, 1944.

and condensation of preexisting connective tissue fibrils, with little evidence of formation of new collager fibers. In fact, the appearance in macrophages of material that gives a positive periodic acid-Schiff reaction may represent active removal of excess ground substance as suggested by Gersh and Catchpole.[19] If this type of myocardial lesion is compared with myocarditis in human pathology, it is seen to be allied morphologically to the toxic myocarditis of diphtheria and, as emphasized by Peschel and associates,[9] to be quite distinct from the process in rheumatic fever.

The histological appearances in the regressive lesions indicated that healing took place mainly by recovery and hypertrophy of partly damaged fibers and condensation of the connective tissue. Areas from which all muscle fibers had disappeared collapsed and appeared compressed by the surrounding muscle. They would probably have condensed into small fibrous scars if followed long enough.

There was no conclusive evidence of the formation of new muscle fibers within the healing lesions. The fibers which appeared to be isolated in connective tissue could be explained by recovery of the atrophic but still viable fibers which were seen within the progressive lesions. Muscle cells which had retained their sarcoplasm had apparently the ability to regenerate myofibrils. The large nuclei and prominent nucleoli in fibers adjacent to both the regressing and the progressing lesions indicated that these fibers had been stimulated in some way, presumably in the latter group by autolytic products of the dead fibers, but these phenomena are also seen at the edges of ischemic lesions in cardiac muscle without any evidence that they are followed by new fiber formation. The consensus from experimental studies is that cardiac muscle does not have the capacity for effective regeneration.[20]

Studies of human diphtheria, on the other hand, have suggested that in this condition the myocardium may possess some regenerative capacity,[21] and the theory of longitudinal splitting of muscle fibers has been put forward to explain the histological appearances in these cases. That the lesion seen in potassium deficiency resembles that in diphtheria has already been stressed, and to some extent the splaying-out of muscle ends and the irregular fasciculation of hypertrophied fibers when cut in transverse section do suggest longitudinal splitting of fibers. This type of lesion differs in important respects from myocardial lesions induced by ischemia or cautery. In the first place, it remains well vascularized throughout its course; secondly, there is no destruction of the connective tissue framework. Under these circumstances it seems that the very restricted powers of regeneration of cardiac muscle may nevertheless lead to partial restitution of structure. From the changes described it appears that this is brought about by hypertrophy of surviving fibers and possibly longitudinal splitting of these fibers to form additional fasciculi in the myocardial syncytium. Outgrowth of new muscle, if it occurs at all, is limited to the bridging of small gaps in fibers which had undergone only a segmental degeneration.

19. Gersh, I., and Catchpole, H. R.: The Organization of Ground Substance and Basement Membrane and Its Significance in Tissue Injury, Disease and Growth, Am. J. Anat. **85**:457-522, 1949.

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SUMMARY AND CONCLUSIONS

1. Myocardial lesions have been produced in less than 12 days in protein-depleted adult rats fed a diet deficient in potassium.

2. Within the area of the lesions there is a primary degeneration of muscle substance which leads to necrosis and disintegration of myocardial fibers. The muscle debris is removed by phagocytes.

3. Secondary to the fiber degeneration there are changes in the connective tissue, consisting of interstitial edema, proliferation of vascular endothelium and fibroblasts, and mobilization of macrophages.

4. If potassium is added to the diet, there is a rapid arrest of the progress of the lesion, and the least severely damaged fibers recover.

5. Healing takes place mainly by hypertrophy of surviving muscle and condensation of the connective tissue. There is no conclusive evidence of effective muscle regeneration.

This study was undertaken at the suggestion of Dr. Paul R. Cannon, who provided the protein-depleted rats for the experiments and made many helpful suggestions and comments. The staining procedures were carried out in Dr. George Gomori's laboratory and I am indebted to him for advice on the techniques used.

RELAPSING MYOSITIS

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AND
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THE PURPOSE of this communication is to record the case of a young man, happily still with us, who, since August, 1950, has had a relapsing febrile illness characterized by the development of numerous tender muscular swellings, protean in distribution, sometimes large in size, almost all of which have completely regressed with restoration of normal function. Examination of the lesions in the muscle indicates that a selective sarcotoxic mechanism is at work. The condition, which we have called relapsing myositis, has many striking and distinctive features and has not, to our knowledge, been previously described.

CLINICAL HISTORY

The patient, a man aged 33, who previously had been healthy, became ill in August, 1950. The illness was characterized by fever and chills, malaise, asthenia, anorexia and stiffness of the legs, followed by stiffness of the arms and shoulders. These symptoms persisted, and about two weeks later there was a transient diarrhea and painful swellings developed in the muscles. At this time he was admitted to the Victoria General Hospital, Halifax. The Gruber-Widal test was negative. The patient was treated with penicillin.

Fever and malaise persisted, and the limbs became painful and the stiffness increased. He was transferred to the care of one of us (R. L. A.) on September 19. On admission, while he stated that he had lost weight with his illness, he was seen to be a well-developed man. There were tender swellings of the muscles. These were present in the right pectoralis major, the left deltoid, the muscles of the forearm on both sides, and in the muscle of the right upper abdominal quadrant. Some of the swellings were large; the largest, the one in the right pectoral muscle, was ovoid and 8 cm. in maximum diameter. The swellings were firm and tender but not warm. There was no edema or erythema over them. Movement of the limbs caused pain in the swellings. Apart from a malar erythema there was no evidence of skin lesions and no edema; in particular, the eyelids were normal. The patient was fevered, with the evening rise of temperature more marked, sometimes being as high as 103 F. There was tachycardia, and a blowing systolic murmur was heard over all cardiac areas. Otherwise the systems were normal.

The only abnormal laboratory findings were (1) an elevated white cell count, always in the vicinity of 15,000 per cubic millimeter and accounted for by a neutrophil leucocytosis without eosinophilia, and (2) an elevated sedimentation rate, 80 mm. in 1 hour (Wintrobe). There was no anemia or hemoconcentration; the hemoglobin content was 14.5 gm. per 100 cc. of blood; the packed cell volume was 40%; the red blood cell count was 5 million per cubic millimeter. Repeated blood cultures (carried out before antibiotic therapy) were sterile; repeated Widal tests were negative. Repeated cultures of the stools and examinations for parasites were negative. The urine was normal. The Wassermann reaction was negative. Eosinophile counts ranged between 125 and 250 per cubic millimeter. Radiological examination of the chest and of bones

From the Department of Pathology, Dalhousie University (Dr. McLetchie) and the Department of Medicine, Victoria General Hospital and Camp Hill Hospital (Dr. Aikens).

revealed no abnormality. An electrocardiogram showed only left axis shift and a sinus tachycardia, with a P-R interval of 0.18 second.

At the end of the first week in the hospital a wedge of the swollen left pectoral muscle was removed. With the report of a myositis of unknown cause, treatment had to be nonspecific. Aureomycin and streptomycin were given over the second week, with no improvement. Then corticotropin (ACTH) was tried over a three-week period, to be followed by cortisone for 24 days more. After corticotropin therapy was begun, there was some general improvement, and the muscle swellings regressed considerably. The original swellings, despite the large size of some of them, had disappeared completely, leaving no apparent functional upset by the end of November, i. e., within 12 weeks after their onset. By the middle of November there was no fever apart from an evening rise in temperature to 99 or 100 F. Some new but small muscular swellings, however, appeared prior to discharge on December 7. Two weeks before discharge, symptoms suggesting ureteral calculus appeared but urological investigation showed nothing of note except bilateral ureteroceles.

After leaving the hospital the patient was seen every fortnight by his family physician. A few new swellings occurred and regressed, and low-grade fever persisted.

On March 12, 1951, he was admitted to Camp Hill Veterans' Hospital, Halifax. The clinical picture was unchanged. His general nutrition and strength were fairly good. Muscle swellings were present in the forearms, various thigh muscles, the calf muscles, and the latissimus dorsi muscles at various periods, some only lasting two or three weeks. A muscle biopsy specimen of a swelling (biceps femoris) was similar to the previous one.

An interesting feature of this admission was the sudden development, on April 20, of a paroxysmal nodal tachycardia, associated with increase in fever and respiratory rate. Quinidine quickly restorted the rhythm to normal, but succeeding electrocardiograms showed a first degree A-V block with a P-R interval of 0.24 to 0.26 second (compared with the tracing of September, 1950, where the P-R interval was 0.18 second). The surmise was that the myocardium had been involved in the same process affecting the skeletal muscles.

Cortisone was administered again in view of previous possible good effects. A protracted course of treatment, with 5.0 gm. of cortisone acetate being given over a three-month period, produced no permanent effect. The low-grade fever remained, and the white blood cell count was still in the region of 15,000 per cubic millimeter, with polymorphonuclear leucocytosis; there was now a slight anemia. The patient was tired and apathetic. By this time, June, 1951, the muscle swellings were limited to small swellings in both biceps muscles, which had not regressed after some months and which prevented complete extension of the forearms; otherwise he had completely free movement. He was discharged to his home in June under the care of his family physician.

When seen in August, 1951, he was feeling better than at any time since the onset of his illness. The temperature, which had been taken regularly at home, still showed a rise each evening to 99 or 100 F. He was still unable to extend his forearms completely, and he complained of pain in the left lower quadrant of the abdomen, which came on with bending. He also complained of palpitation and shortness of breath. On examination there was nothing new in his general make-up. His strength and nutrition were good. There was possibly some shortening of the biceps on both sides, due to fibrosis and contraction, and small hard lumps were still present. There was a mass, 5 cm. in diameter, in the left iliopsoas muscle, which accounted for his abdominal discomfort; firm muscle masses, 2 to 4 cm. in diameter, were also noted in the right latissimus dorsi muscle, the right brachioradialis muscle, and in the adductors of the left thigh. Electrocardiograms still showed a first degree A-V block.

Radiographic examination of muscle, joints, skeleton, and alimentary tract showed no abnormality. His temperature and pulse were normal; the sedimentation rate was 15 mm. in 1 hour; the hemoglobin content, 11 gm. per 100 cc.; the white blood cell count, 15,000 per cubic millimeter with polymorphonuclear leucocytosis but no eosinophilia.

The patient was last seen in November, 1951. He had gained 20 lb. (9 kg.) since August, 1951, and his strength and general condition were good. There was further improvement in his ability to extend the forearms. The swellings noted in August had disappeared except those in the right brachioradialis and the adductors of the left thigh, which had diminished. In addition, there was a nontender swelling in the left iliacus, and there were tender swellings in the left

flexor carpi ulnaris, right obliquus externus abdominis at the level of the ninth rib, and the medial head of the gastrocnemius. His temperature was normal, the white blood cell picture was within normal limits apart from slight eosinophilia (875 eosinophiles per cubic millimeter); the sedimentation rate was still elevated (23 mm. in 1 hour, Wintrobe). The electrocardiogram was unchanged. Apart from the muscular swellings he had no complaints, and physical examination did not reveal any other abnormality. It was apparent that there had been progressive diminution of the severity of the condition.

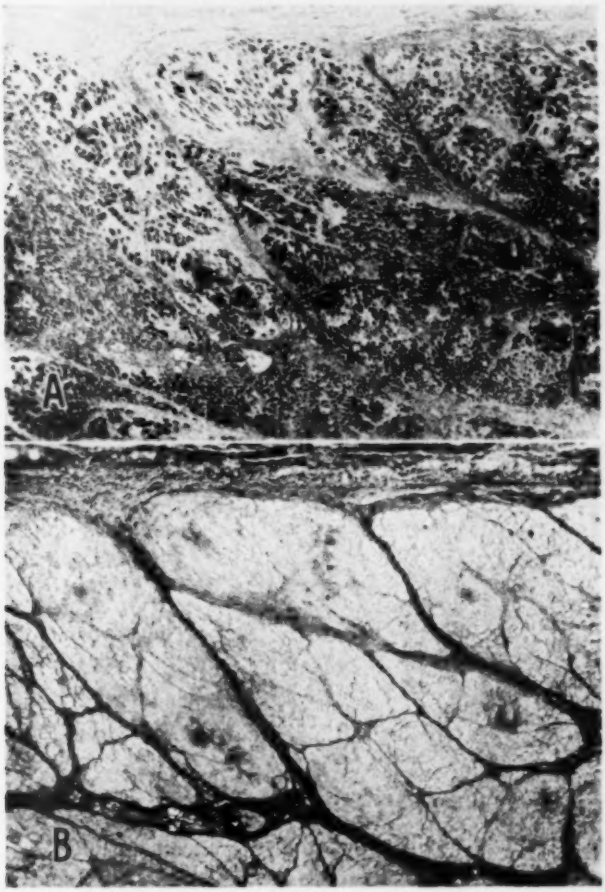

Fig. 1.—*A* and *B*, thickening of septa and patchy disappearance of muscle fibers; dark smudges are foci of pannecrosis. Different filters; modified Mallory stain; × 14.

MUSCLE BIOPSIES

A large wedge of the original swelling in the right pectoral muscle was removed; it was sufficient to make 15 blocks, each approximately 1 sq. cm. in section and 0.5 cm. in thickness. Paraffin sections were made from the majority of the blocks;

a few were examined by means of frozen sections. The blocks were examined by serial or step section. The lesion encountered was remarkably uniform, however, and little variation was present throughout the tissue. The same obtained for the second biopsy.

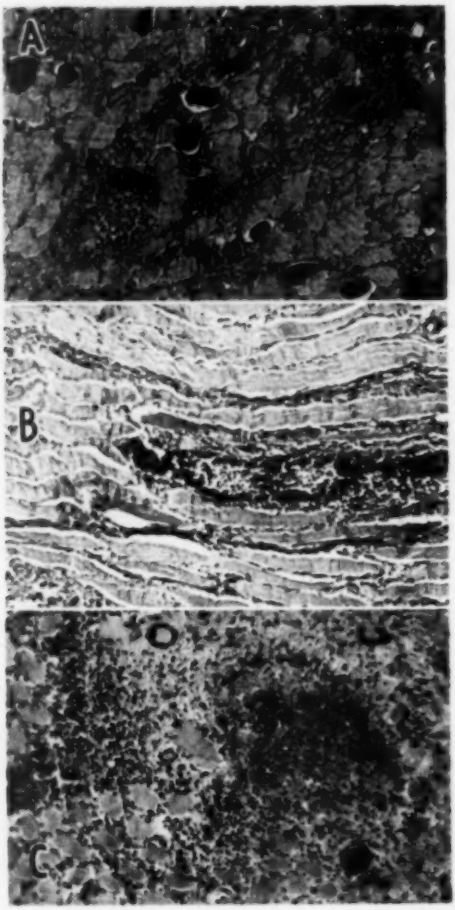

Fig. 2.—*A*, patchy necrosis. The dark swollen fibers show complete hyaline necrosis. Modified Mallory stain; × 75.

B, complete necrosis of muscle fibers. A cellular infiltrate replaces the central fibers. Hematoxylin-eosin stain; × 75.

C, focus of pannecrosis surrounded by palisaded histiocytes, including giant cells. Hematoxylin-eosin stain; × 75.

To the naked eye the muscle is pale and broken up by whitish lines to form a fine cobweb pattern.

Low-power microscopic examination of sections shows generalized thickening of the epimysium and the perimysium, a patchy replacement of muscle fibers by a cellular infiltrate, and small smudge-like foci of pannecrosis (Fig. 1). The thickening of the epimysium and the perimysium is due, in small part, to edema, prominence of fibroblasts, and some increase of collagenous fibrils but mainly to round cell infiltration. The infiltrate consists of lymphocytes and histiocytes with occasional neutrophile and eosinophile leucocytes.

Muscle Necrosis.—There is widespread patchy necrosis of muscle fibers involving approximately 15% of the fibers. The necrosis is uniform in character, proceeding through karyolysis, swelling, and loss of striation to the production of swollen hyaline and acidophilic fibers. Dead fibers lie among healthy ones (Fig. 2).

Pannecrosis.—Foci of pannecrosis are present in every section. They are small and fairly uniform in size and lie in the centers of the bundles. They consist of a conglomerate of intensely acidophilic dead fibers intermingled with necrotic cellular infiltrate and interstitium. In older lesions there is palisading of histiocytes at the periphery (Fig. 2*C*).

Local Mesenchymatous Reaction.—As is evident from all the illustrations, the necrosis of the muscle has called forth a vigorous local cellular response and damaged muscle is being rapidly absorbed and replaced by sheets of histiocytes, including occasional giant cells. Apart from the foci of pannecrosis, the necrotic process is confined to the muscle substance, and reticulin preparations reveal most of the sarcolemma pattern of fibers showing early necrosis to be intact and to stain normally. Breaches of the sarcolemma are associated with round cell infiltration of the dead fibers.

Follicular Lesions.—The integrity of the mesenchymal investment of the dead fibers and the retention in varying degrees of the sarcolemma in the presence of necrosis of muscle substance has led in many instances to the production of striking lesions. These consist of follicles which represent swollen necrotic muscle fibers, outlined by the sarcolemma, in which the sarcous substance has been replaced by histiocytes and leucocytes. While, following the work of Metchnikoff on the absorption of the tail of the tadpole, there are in standard texts numerous references to histiocytes of sarcolemmal origin, as far as can be judged, the histiocytes, as do the leucocytes, originate in the interstitium and migrate through breaches in the sarcolemma. There they proliferate and form a layer closely applied to the inner aspect of the sarcolemma; later they proliferate and migrate to fill the sarcolemmal tube as the sarcous substance is absorbed (Figs. 3 and 4*A* and *B*). In longitudinal section this type of lesion may involve only part of the fiber, the remainder being viable. When the process is completed there may be loss of sarcolemmal outlines leaving a mosaic of histiocytes with slight and irregular laying-down of reticulin (Fig. 4*C*).

Vasculoexudative Reaction.—Some fibrin threads are present in the foci of pannecrosis; otherwise the leucocytic infiltrate, scanty and masked by the histiocytic response, is the only evidence of exudative reaction apart from occasional foci of eosinophile leucocytic infiltration around dead fibers.

Blood Vessels.—These are normal. In particular, serial sections of areas of pannecrosis and the use of stains for elastic tissue show no evidence of specific

vascular lesions. In addition, there is no evidence of proliferation of blood vessels as one might expect from the granuloma-like appearance of the lesion.

Nerves.—Those in the epimysium are normal. In the endomysium some smaller bundles show acute degeneration with fatty change and demyelination. There is no

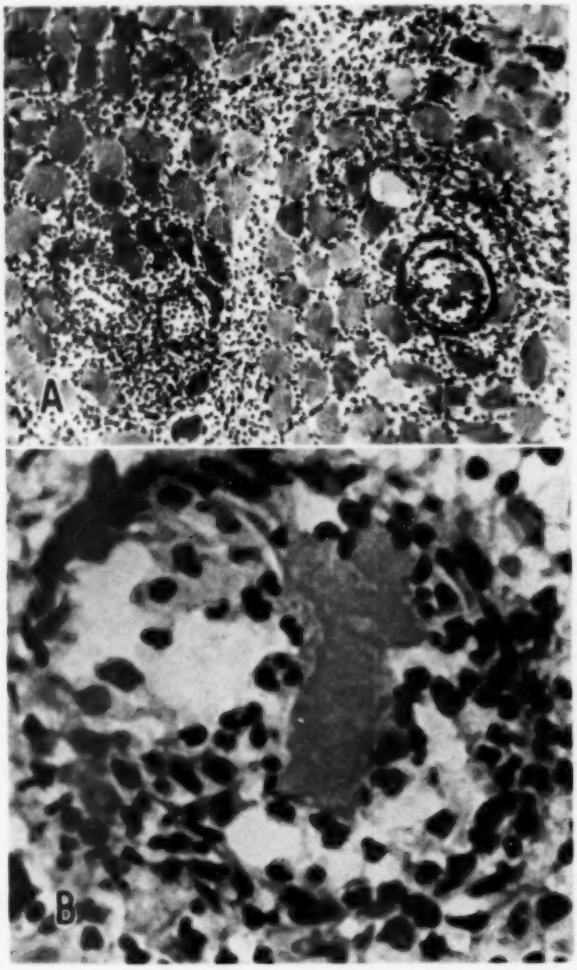

Fig. 3.—*A*, interstitial infiltrate and follicular lesions. Sarcous substance is still present in the ringed follicle. Hematoxylin-eosin stain; × 125. *B*, high magnification of the ringed follicle of *A*. The follicle still contains sarcous substance undergoing active phagocytosis.

evidence of primary neuritis in the form of vascular congestion, round cell infiltration, and neurilemmal proliferation within the nerve bundles.

Fibrinoid Degeneration of Collagen.—It is not present.

Micro-Organisms.—Glynn's stain, Kirkpatrick's saline-Gram [1] technique, the periodic acid-Schiff reagent, eosin-methylene blue, and a great variety of trichrome stains show no evidence of micro-organisms or inclusion bodies.

Regeneration of Muscle.—This is slight and similar to that encountered in cases of dermatomyositis.

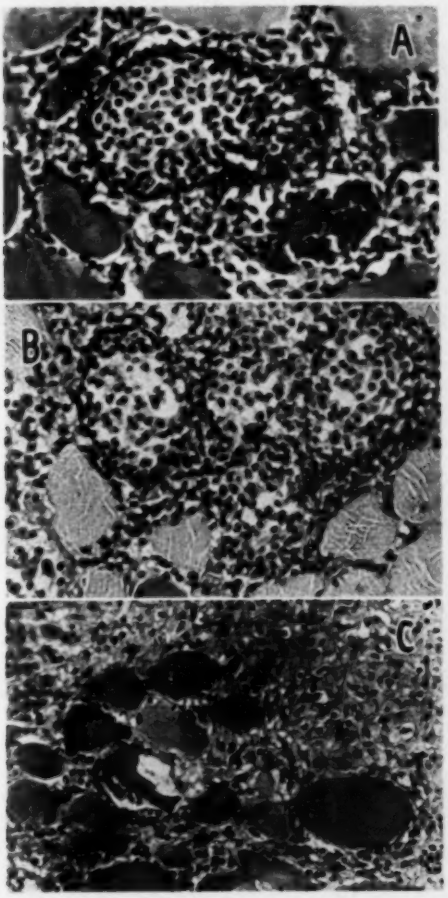

Fig. 4.—*A*, follicle of histiocytes defined by the sarcolemma. A smaller follicle losing its outline but still containing sarcous substance is also seen. Hematoxylin-eosin stain; × 225.

B, conglomerate of follicles almost losing their distinction. Hematoxylin-eosin stain; × 225.

In *C*, the follicular pattern has gone, leaving a mosaic of histiocytes. The muscle fibers show hyaline necrosis. Modified Mallory stain; × 200.

1. Browning, C. H., and Mackie, T. J.: Textbook of Bacteriology, London, Oxford University Press, 1949, p. 781.

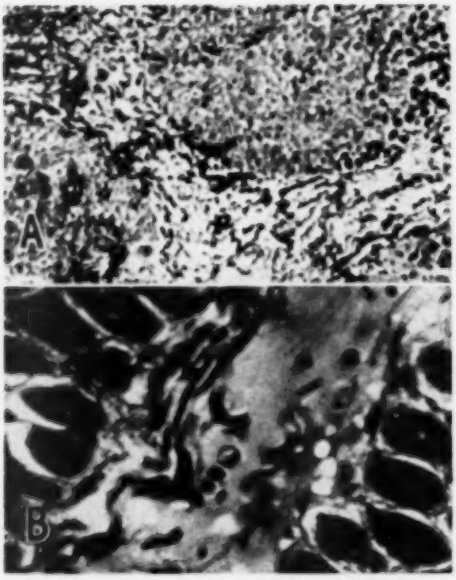

Fig. 5.—*A*, interstitial edema and fibrinoid degeneration of collagen (dark fibrils). The muscle cells are swollen and pale, and their nuclei are swollen, pyknotic, and centrally placed. Note the paucity of cellular infiltrate in this and all succeeding illustrations. Modified Mallory stain; × 75.

B, fibrinoid degeneration of collagen (dark fibrils) and revelation of ground substance (granular matrix). The muscle fibers show hyaline necrosis. Modified Mallory stain; × 500.

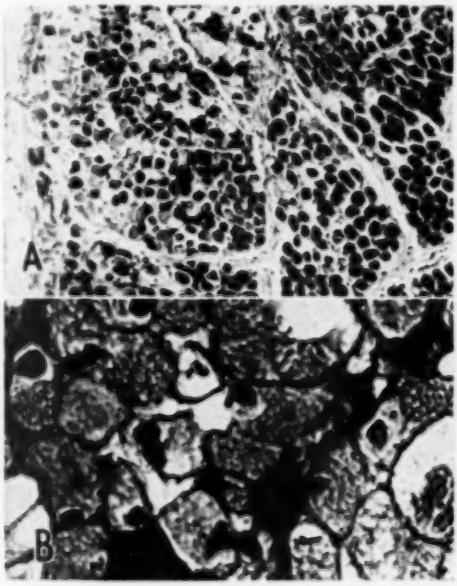

Fig. 6.—*A*, lytic necrosis. The sarcous substance is becoming pale and disappearing, leaving empty sheaths. Eosin-phloxine-tartrazine stain (Lendrum, A. C.: The Phloxin-Tartrazine Method as a General Histological Stain and for the Demonstration of Inclusion Bodies, J. Path. & Bact. **59**:399-404, 1947); × 125.

B, higher magnification of a field of *A* showing swollen fibers, swollen, pyknotic nuclei, and intracellular edema; × 600.

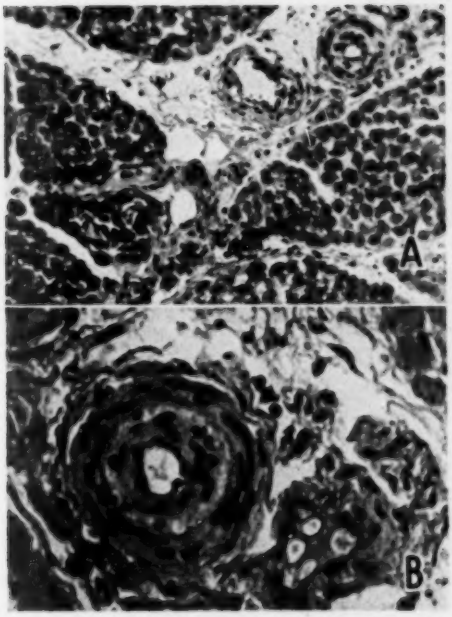

Fig. 7.—*A*, edema and infiltrate in interstitium. One vessel shows proliferative change. Hematoxylin-eosin stain; × 125.

B, high magnification of a vessel in *A* showing increase and radial arrangement of endothelial nuclei and intimal proliferation of cells; × 360.

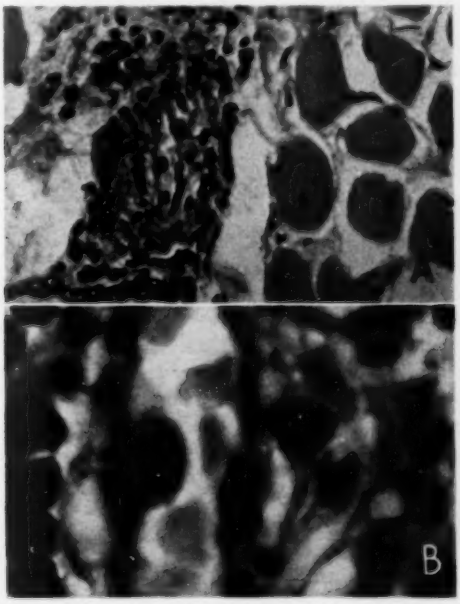

Fig. 8.—*A*, vasculitis and perivascular infiltrate. Hematoxylin-eosin; × 420.

B, higher magnification of a part of the vessel in center of *A*. Note the proliferation of endothelium presenting as a bud-like cell projecting into the lumen; × 1600.

COMPARISON WITH DERMATOMYOSITIS

The sections have been compared with sections of muscle specimens taken for biopsies from four patients with dermatomyositis in the acute phase. All these were children and their condition was characterized by prolonged sore throat, generalized edema, and muscular weakness. Our findings are in general agreement with those of Pagel, Woolf, and Asher [2] and present the following striking differences from relapsing myositis: 1. The muscle necrosis is protean in character, showing lysis of fibers to leave empty sheaths, as well as areas of hyaline necrosis; grossly swollen, centrally placed, pyknotic nuclei may be prominent in degenerate fibers (Figs. 5 and 6). 2. Fibrinoid degeneration of collagen and revelation of the ground substance of collagen are conspicuous (Fig. 5*A* and *B*). 3. Vascular lesions are prominent, affect vessels of all sizes, and vary from acute fibrinoid to proliferative lesions (Figs. 7 and 8). 4. Local mesenchymal response and vasculoexudative response to the acute phase of muscle damage are conspicuous by their paucity and are mainly confined to small perivascular cuffs of mesenchymal cells not specifically differentiated, in contrast with the vigorous and healthy histiocytic response in the relapsing myositis (Figs. 7*A* and 8*A*). 5. No follicular lesions are present. Thus in dermatomyositis there is involvement of collagen and blood vessels as well as of muscle in the morbid process, and the lack of cellular response in the acute phase is further indication of a sickness of the mesenchyme. This contrasts with relapsing myositis, in which the morbid mechanism is specifically sarcotoxic and the mesenchymal investment of the muscle is conspicuously healthy.

COMMENT

The abrupt onset, the muscular swellings, the absence of cutaneous edema and erythema, the fever and the high leucocytosis, the prolonged relapsing character of the disease are all at variance with the clinical course of dermatomyositis [3] and indeed with any recorded myositis. This unique character is also strikingly demonstrated by the quality of the muscular lesions, where the only factor in common with dermatomyositis is the presence of necrosis of muscle, and even here there are differences.

Pains have been taken to exclude polyarteritis nodosa or any other arteritis which might conceivably have produced the clinical condition. The question of a functional vascular disturbance, vasospasm, has also to be considered. The absence of cramp-like pains with the initiation of the lesion and of vascular disturbance in the overlying skin is not in keeping with a vasospastic condition. Furthermore, the pathological picture could conceivably be in keeping only with spasm of the smallest vessels since there is no evidence of an infarctive condition en masse; at the level of small vessels the collateral supply is too abundant to consider any question of vasospasm. Again a large amount of muscle has been available for examination and we can conclude that with routine methods of examination no micro-organisms can be identified. In addition the clinical history does not suggest any known infection.

2. Pagel, W.; Woolf, A. L., and Asher, R.: Histological Observations on Dermatomyositis, J. Path. & Bact. **61**:403-411, 1949.

3. O'Leary, P. A., and Waisman, M.: Dermatomyositis: A Study of 40 Cases, Arch. Dermat. & Syph. **41**:1001-1009 (June) 1940.

A remarkable feature of the clinical condition is the complete resolution, with restoration of normal function in all but two of the muscular lesions. The fact that the patient has maintained his weight and strength and that the symptoms have been confined to muscle hardly allows the consideration of a more generalized toxic process with special effects on muscle. Clearly the fever, the leucocytosis, and the high sedimentation rate can reasonably be regarded only as secondary to the muscle damage. The pathological study of the muscle indicates that an acute hyaline and patchy necrosis of muscle fibers has been followed by a vigorous response of the local mesenchyme to produce an intense histiocytic proliferation with rapid removal of the damaged sarcous substance. In many fibers the necrosis of the muscle has been so selective that even the sarcolemma has remained largely intact to produce striking follicular lesions, as the histiocytes, ringed by the sarcolemma, replace the sarcous substance. The complete resolution and restoration of function are further evidence of the integrity of the mesenchyme, since restoration of function is possible only with rapid removal of damaged products. From the above we may infer that the foci of pannecrosis merely result from the liberation of products of acute necrosis of the sarcous substance acting on the adjacent integument. Thus a combination of clinical and pathological evidence indicates that the noxious mechanism acts over a given area of muscle for a short period, has no continuing action in that area, and affects only the sarcous substance. Moreover, the cause of the necrosis is not to be sought outside the muscle by ordinary methods of examination, and the symptoms may all be readily attributed to the necrosis of the sarcous substance. In other words, while the nature of the morbid mechanism is unknown, we can surely classify the condition as a true idiopathic or essential myositis. Moreover, since the onset of the illness there has been progressive diminution in the severity of the condition, and, so far, no individual muscle has been affected more than once. All of which confers a striking and unique individuality on the condition. The permanent nature of the heart block can reasonably be attributed to necrosis involving conduction bundles. The condition suggests a disorder of the specific enzymes of muscle or the production of autoantibodies to sarcous substance.

To our knowledge no similar syndrome has been described in the literature. In the earlier German literature there is a classification of myositis in which Group I refers to a primary, or essential, idiopathic myositis.[4] We can find no detail of such a case, however, except that in the literature one encounters the term "myositis fibrosa." According to Batten,[5] myositis fibrosa starts as a subacute inflammation of muscle and leads to a slowly progressive chronic myositis with retraction and deformity. The general condition of the patient is but little disturbed; there is no fever, no edema, and no cutaneous erythema. In some cases the affected muscles become swollen so that a hard solid tumor develops, which involves the skin and surrounding tissues. Pathologically there are interstitial fibrosis and fibrous replacement of muscle. To our knowledge more acute lesions have not been described. While the condition may be related to relapsing myositis, descriptions of the pathologic aspects of the condition are vague.

4. Fahr, T.: Zur Frage der Polymyositis (Dermatomyositis), Arch. Dermat. u. Syph. **130**:1-14, 1921.

5. Batten, E. F.: Case of Myositis Fibrosa, with Pathological Examination, Tr. Clin. Soc. London **37**:12-22, 1904.

SUMMARY

The case is described of a young man, still with us, who over the course of 17 months, has had a relapsing febrile illness characterized by the development of numerous tender muscular swellings, protean in distribution, sometimes large in size, almost all of which have completely regressed with restoration of normal function. A permanent heart block has also developed during the course of the illness. The condition is becoming less severe, and the patient maintains his weight and muscular power.

The pathologic appearance of the skeletal muscle, in conjunction with the complete resolution of the lesions and the restoration of function, is indicative of the action of a selectively sarcotoxic mechanism which acts in any area only over a short period.

The condition, which has many striking and distinctive features and has not been previously described, has been designated relapsing myositis.

NOTE.—Since the Coxsackie virus [6] produces in suckling mice an acute myositis identical with the acute stage of our relapsing myositis, specimens of feces, serum, and muscle lesions were sent for identification of Coxsackie infection to Dr. A. C. Rhodes, University of Toronto. While the investigation continues, reactions to all tests so far have been negative.

6. Gifford, R., and Dalldorf, G.: The Morbid Anatomy of Experimental Coxsackie Infection, Am. J. Path. **27**:1047-1064, 1951.

ANOMALOUS OCCIPITAL APERTURES

RONAN O'RAHILLY, M.B., B.Ch., M.Sc.
DETROIT

ANOMALOUS apertures of the occipital bone are not encountered frequently. The case presented below may serve as an introduction to a discussion of the types of occipital opening found associated with cranial meningo(encephalo)cele and dermoid cyst. Brief reference will then be made to some recent views on spina bifida, because bifid vertebral arches and defective occiput are both median deficiencies in the skeletal dorsal wall of the central nervous system. Since large openings are sometimes found also in the parietal bones at the sites of the normal parietal foramina, the occurrence of a similar normal vascular canal in the occipital bone will be pointed out. Finally, the development of the occipital bone will be summarized, with a view to describing occipital apertures in terms of embryology.

A CASE OF OCCIPITAL MENINGOCELE

Clinical Examination.—Mr. Warwick Bailey, F.R.C.S., Scunthorpe War Memorial Hospital, England, has supplied the following particulars: A boy aged 10 years was referred to Mr. Bailey because of a lump on the back of his head which had been noticed since birth. Both the child's mother and the family physician considered that it was becoming larger. The swelling was painful when touched. On examination there was a cystic prominence over the occipital bone in the posterior median line. It was found that compression of the neck caused an increase of pressure in the swelling. The hair was cut shorter, and at an interview 10 months later symptoms were not complained of.

Radiological Examination (Fig. 1).—Dr. Thomas Lodge, F.F.R., Sheffield Royal Hospital, furnished skiagrams of this case. The occipital bone shows thinning in its upper part, and a circular bony defect is present in the median plane, below the protuberance. A minute cleft-like extension proceeds upward from the opening and is also median in location.

CRANIAL MENINGO(ENCEPHALO)CELE AND DERMOID CYST

A number of cases of ("sub")occipital meningocele or meningoencephalocele have been reported. According to Houels (cited by Pape,[1] 1928), out of 93 cranial meningoceles, 68 (73%) were occipital, 16 (17%) frontal, and 9 (10%) basal. Occipital meningoceles occur in or near the median plane, but the level varies, as can be seen from the following reports.

From the Department of Anatomy, Wayne University.

1. Pape, L.: Ein Fall von Meningocystokele, Zentralbl. Gynäk. **52**:2040-2041, 1928.

Girardier [2] (1939) described a meningoencephalocele which was observed in a boy aged 2½ months. The cranial opening was situated above the external occipital protuberance, whereas, he pointed out, it is usually located at the level of or below the protuberance. In Macphail's [3] (1931) case a girl aged 3 months showed "a pedicle, about a fingerbreadth in thickness" issuing "from the occipital fontanelle." There is no illustration, but the fonticulus posterior (B. R.) or occipitalis (B. N. A.) is situated at the lambda. In a case of meningocele illustrated by Pancoast, Pendergrass, and Schaeffer [4] (1940) the cranial defect "is in the location of the torcular Herophili [confluens sinuum, B. R., B. N. A.] and measures 1 cm. in diameter." The skiagram resembles closely Figure 1 of this paper. Pape (1928) featured one that was observed in a very abnormal fetal skull. The bony opening was "immedi-

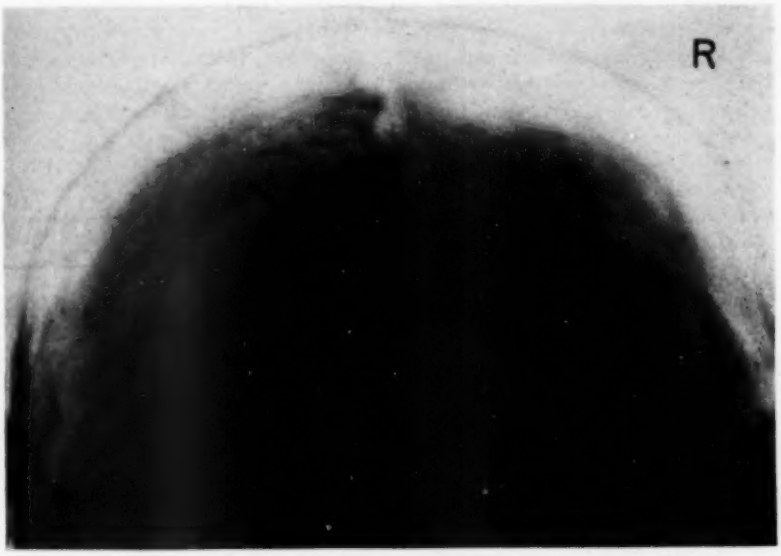

Fig. 1.—Skiagram of a cranial vault showing a median occipital aperture. A cleft-like extension proceeds craniad. The aperature was associated with an occipital meningocele.

ately under the occipital protuberance." Shallow [5] (1928) reported five cases of meningo(encephalo)cele of the occipital region in infants. In one the bony defect was the size of the tip of an index finger and was situated "to the right of the midline, between the foramen magnum and occipital protuberance." Partial cerebellar prolapse had occurred in two of the cases. In one of these instances, in which the aperture was "in the occipital bone to the left of the midline," the left temporal

2. deGirardier, M. J.: Un cas de méningo-encéphalocèle occipitale chez un nourrisson de 2 mois ½, Lyon chir. **36**:180-183, 1939.

3. Macphail, R. M.: A Large Occipital Meningocele, Brit. M. J. **1**:179-180, 1931.

4. Pancoast, H. K.; Pendergrass, E. P., and Schaeffer, J. P.: The Head and Neck in Roentgen Diagnosis, Springfield, Ill., Charles C Thomas, Publisher, 1940, Fig. 71.

5. Shallow, T. A.: Spina Bifida and Cranial Meningocele, Ann. Surg. **87**:810-822, 1928.

bone and left half of the occipital bone were smaller than those of the right side. Hacke [6] (1951) recorded a case of meningoencephalocystocele in which the cranial defect occurred in the squamous occipital bone below the protuberance. West's [7] (1875) patient (aged 1½ years) had a 2- by 1-in. bony opening which "extended from the foramen magnum backwards almost to the occipital protuberance" and also presented cervical spina bifida. Latto's [8] (1942) patient (a woman aged 33), with a meningocele "about the size of half a hen's egg in the midline just below the occiput," had a cervical spina bifida and vertebral fusion (Klippel-Feil syndrome). In Fulcher's [9] (1933) case of suboccipital meningocele in an infant aged 5 months, "the bony defect of the occipital bone extended into the foramen magnum." Gabriel and Paul [10] (1928) found "an absence of the squamous portion of the occipital bone" in their case of occipital meningocele in a man aged 23. Schreiber [11] (1930) described a suboccipital meningocele (in a woman aged 21) which, by providing decompression, masked the symptoms of an apparently unrelated left occipital brain abscess. The cranial opening, 1.5 cm. in diameter, was "in the midline of the occipital bone." Other cases have been featured by Livingston [12] (1923), Penfield and Cone [13] (1932), Aloi [14] (1934), Micca [15] (1938), Santanelli [16] (1940), Santanelli and Fontana [17] (1942), Babbini and Stelzer [18] (1942), and Scoville and McLaurin [19] (1951).[20] The case of lacunae in the "superior occipital

6. Hacke, W.: Seltene angeborene Schädelspaltmissbildungen bei Neugeborenen, Zentralbl. allg. Path. **87**:26-34, 1951.

7. West, J. F.: Case of Meningocele Associated with Cervical Spina Bifida, Cured by Aspiration, Lancet **2**:552-553, 1875.

8. Latto, D.: A Case of Klippel-Feil Syndrome, Brit. M. J. **1**:669, 1942.

9. Fulcher, O. H.: Removal of Suboccipital Meningocele with Cure, J. A. M. A. **100**:257-258, 1933.

10. Gabriel, V., and Paul, M.: A Case of Occipital Meningocele, J. Ceylon Br. Brit. M. A. **25**:66, 1928.

11. Schreiber, F.: Suboccipital Meningocele Masking Symptoms of Brain Abscess: Report of a Case, J. Michigan M. Soc. **29**:433-434, 1930.

12. Livingston, J.: Suboccipital Meningocele Successfully Removed, Brit. M. J. **1**:508, 1923.

13. Penfield, W., and Cone, W.: Spina Bifida and Cranium Bifidum: Results of Plastic Repair of Meningocele and Myelomeningocele by a New Method, J. A. M. A. **98**:454-461, 1932. Poirier, M., and Charpy, A.: Traité d'anatomie humaine, Ed. 3, Paris, Masson & Cie, 1920, Vol. 2, Pt. 3.

14. Aloi, V.: Contributo allo studio d'una rara Malformazione congenita della testa, Ann. ital. di chir. **13**:219-226, 1934.

15. Micca, A. B.: Sopra un caso di meningocele occipitale, Ginecologia **4**:25-40, 1938.

16. Santanelli, L.: Meningoencéfalocele occipital, Bol. Soc. cir. Rosario **7**:400-407, 1940.

17. Santanelli, L., and Fontana, G.: Un nuevo caso de meningoencéfalocele occipital, Bol. Soc. cir. Rosario **9**:153-158, 1942.

18. Babbini, R., and Stelzer, C. P.: Meningocele occipitoparietal, Bol. Soc. cir. Rosario **9**:127-130, 1942.

19. Scoville, W. B., and McLaurin, R. L.: Tantalum Mesh in Repair of Congenital Bony Defects of Skull and Spine, J. A. M. A. **147**:639-640, 1951.

20. Dr. Scoville has informed me that he has recently removed a huge encephalocele (twice the size of the head) from a newborn girl. "The skull defect lay in the exact midline approximately a centimeter or two above the foramen magnum, and the defect measured some 1.5 to 2 cm. in diameter, lying approximately at the superior portion of the dorsal cerebellum. Through this defect I could see the concave undersurface of the tentorium. Hence, it must have lain just below the occipital protuberance." Dr. Scoville states that the bony defect published by him and Dr. McLaurin was in a similar location.

cranial wall" described (but not illustrated) by Pommé, Marot and Tanguy [21] (1935) is presumably an instance of foramina parietalia permagna.

Hartley and Burnett [22] (1944) reproduced the skiagram of an occipital bone from a case of craniolacunia (*Lückenschädel*) in a hydrocephalic stillborn fetus. It is of present interest in that it shows a transversely oval fenestra in the region of the inion and to the left of the median plane, which is "not unlike those through which encephaloceles protrude." A number of cases of combined meningocele and craniolacunia have been recorded, but the meningocele need not be cranial. Thus, Doub and Danzer [23] (1934) described two such combinations in newborn infants, one of which had a lumbar, and the other a thoracic, meningocele. Vogt and Wyatt [24] (1941) found that of 120 meningocele patients, 43% showed craniolacunia, whereas the latter condition was noted in only two of the remaining group of more than 5,000 skull films of patients without meningocele. The additional complication of craniolacunia appeared to affect the prognosis of meningocele adversely. Pressure theories seem to be out of fashion at present for craniolacunia (Hartley and Burnett,[22] 1944; van Doorn and Boet,[25] 1949), but little is known concerning the condition.

An occipital aperture similar to that found in cases of meningocele has been recorded in instances of intracranial dermoid cysts in this region. Thus, Kwan [26] (1930) found, in a girl aged 19, "a perforation of the occipital bone just below the external occipital protuberance to the left of the midline" through which passed the pedicle of a 5-cm. dermoid cyst lying between the cerebellar hemispheres, the pedicle fusing with the deep surface of the scalp. Charest [27] (1943) found, in a boy aged 3, an infected 3-cm. dermoid cyst and "extensive ossification abnormalities of the cervical spine amounting almost to a Klippel-Feil syndrome, a congenital ossification defect in the midline of the occipital bone [corresponding to the soft tissue protrusion] and evidence of generalized increase in intracranial pressure." Gladstone [28] (1937) described, in a girl aged 1 year, a degenerating cerebellar dermoid cyst which ended "in a round smooth cavity in the occipital bone, midline, just below the external occipital protuberance," and from this 2-cm. cavity "a small probe could be passed through a small hole communicating with the deep subcutaneous tissues of the scalp." Other cases were described by Ogle, Lannelongue, and Archard, and Ruschaupt (see Brock and Klenke,[29] 1931, and Charest,[27] 1943). Charest failed to trace a case said to have been featured by Cushing.

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21. Pommé, B.; Marot, R., and Tanguy, R.: Lacunes symétriques et congénitales de la paroi cranienne occipitale supérieure, Lyon méd. **155**:14-18, 1935.

22. Hartley, J. B., and Burnett, C. W. F.: New Light on the Origin of Craniolacunia, Brit. J. Radiol. **17**:110-114, 1944.

23. Doub, H. P., and Danzer, J. T.: Lückenschädel of the Newborn, Radiology **22**:532-538, 1934.

24. Vogt, E. C., and Wyatt, G. M.: Craniolacunia (Lückenschädel), Radiology **36**:147-153, 1941.

25. van W. Doorn, C., and Boet, J. N.: Lacuna Skull and Craniofenestria, Am. J. Dis. Child. **77**:315-327, 1949.

26. Kwan, S. T.: Intracranial Dermoid Cyst, Arch. Neurol. & Psychiat. **24**:1292-1293, 1930.

27. Charest, F.: Kyste dermoïde intra-et extracrânien de la région occipitale, J. Hôtel-Dieu Montréal **12**:73-88, 1943.

28. Gladstone, N. H.: Intracranial Dermoid: Case Report, J. Indiana M. A. **30**:282-284, 1937.

29. Brock, S., and Klenke, D. A.: A Case of Dermoid Overlying the Cerebellar Veins, with a Review of the Literature on Intracranial Dermoids, Bull. Neurol. Inst. New York **1**:328-342, 1931.

We may conclude that the cranial defects associated with occipital meningo-(encephalo)celes or dermoid cysts tend to occur in or near the median plane and are situated (*a*) rarely above the occipital protuberances (even as high as the lambda), (*b*) sometimes at the occipital protuberances, or (*c*) most commonly between the protuberances and the foramen magnum. The defect may extend into the foramen magnum and may be associated with cervical spina bifida. The embryology of these locations will be discussed later.

CRANIUM BIFIDUM AND SPINA BIFIDA

It can be seen, then, that abnormally large openings in or near the occipital protuberances generally seem to transmit the stalk, closed or open, of a meningocele or a dermoid cyst. According to Pancoast and associates [4] (1940), "in the posterior fossa, emissary veins at the torcular Herophili [confluens sinuum, B. R., B. N. A.] and stalks of dermoid cysts may simulate the appearance found in meningocele." In this respect occipital apertures differ from foramina parietalia permagna, the presence and the size of which can in no way be correlated with the structures (a few vessels) they may transmit. It does not follow, of course, that these occipital openings are caused by the presence of a connecting stalk, any more than that the combined intracranial and extracranial nature of the swelling is due to the bony defect. Greig [30] (1927), who made a particularly detailed study of large parietal foramina, pointed out that "an opening due to [sic] tumour is much more common in the occipital than in either of the parietal bones, and even though the tumour does not protrude the bone over it may be deficient." His view was that "an opening in the skull where no opening should be as in the planum occipitale in Turner's case [see below] may be prima facie evidence of a congenital tumour, but a deficiency at the site of a normal foramen is prima facie evidence of congenital largeness."

According to Spring's theory (see Aloi,[14] 1934, and Micca,[15] 1938), an arrest of development of a cranial bone or an inflammatory process of the meninges or a precocious ossification of a suture results in a dural-arachnoid adhesion which is followed by edema, cranial perforation, and secondary herniation. Although this view is commonly spoken of as abandoned, the idea of secondary herniation is not foreign to recent views on spina bifida (see below). Meckel and a number of other authors believed that herniation does not occur but that a failure of cranial development takes place around the embryonic brain and meninges. This was regarded as similar in production to a failure of vertebral development in spina bifida. Keen [31] (1948), however, believes that *all* cases of spina bifida (he is discussing cranial defects, also) are due to cerebrospinal fluid disturbances, resulting in neural destruction and splitting open of the neural tube and/or its dorsal coverings. It is of historical interest to recall that Morgagni (1682-1771) associated spina bifida with hydrocephalus and attributed both to occlusion of the central canal of the spinal cord (Fraser,[32] 1929). Shallow [5] (1928) maintained that "increased pressure of the cerebrospinal fluid does not seem to be as potent a factor in the production of cranial defects as some think it to be in the development of spinal

30. Greig, D. M.: Abnormally Large Foramina Parietalia, Edinburgh M. J. **34**:629-648, 1927.

31. Keen, J. A.: The Genesis of Spina Bifida and Allied Congenital Defects, Clin. Proc. **7**:162-172, 1948.

32. Fraser, J.: Spina Bifida, Edinburgh. M. J. **36**:284-310, 1929.

anomalies." Ströer and Zwan [33] (1939) consider that, in addition to excessive production of cerebrospinal fluid resulting in local enlargements of the closed neural tube and subsequent degeneration of the tube wall, nonclosure of the neural plate (followed by neurodegeneration) due to abnormalities of the underlying mesoderm is a cause of spina bifida, in some cases. Patten [34] (1946) favors local overgrowth of the neural tube interfering with closure. A discussion of relevant experimental embryology (see Gillman and associates,[35] 1948, for example) would be outside the scope of this paper.

A particularly interesting case of cranial openings is that described by Turner [36] in 1865 and subsequently reexamined by Greig [30] (1927) (referred to above). Here, in a woman aged 25, two large parietal foramina (measuring 18 by 9 and 21 by 14 mm. on the left and right sides, respectively) were accompanied by a median occipital aperture in the interparietal region measuring 14 by 25 mm. This was narrowed by membrane and transmitted the closed stalk of a meningocele. The cyst had been present at least since childhood and was the size of a hen's egg; its removal resulted in fatal meningitis.

APERTURES IN THE CRANIAL VAULT

In addition to occurring at abnormal sites, cranial defects may also appear as persistent or unusually large openings at normally patent loci, such as fontanels or foramina. Thus, unusually large openings may be found at the sites of the parietal foramina (foramina parietalia permagna or fenestrae parietales symmetricae) and have been the subject of much discussion (see O'Rahilly and Twohig,[37] 1952); they transmit at most a few minute vessels. In the occipital region additional sutures are of relatively frequent occurrence, but large foramina are rare. The occipital emissary vein (v. emissaria occipitalis, B.R.; emissarium occipitalis, B.N.A.) is a small vein which unites the confluence of the sinuses with the occipital veins; it traverses the occipital bone in the region of the protuberances and communicates with the occipital diploic vein (v. diploica occipitalis, B.R., B.N.A.) (Poirier and Charpy,[38] 1920). A vein which could be traced distinctly through the bone was found in only 6 (13.6%) of 44 dissections (Knott,[39] 1881). In examining 512 skulls Sperino found a canal (*canal inio-endiniaque*) present (single or multiple) in 226 (44%), completely absent in 39 (8%), and present only as an

33. Ströer, W. F. H., and van der Zwan, A.: Anencephaly and Rachischisis Posterior, with Description of a Human Hemicephalus of 18 mm., J. Anat. **73**:441-450, 1939.

34. Patten, B. M.: Embryological Stages in the Development of Spina Bifida and Myeloschizis; abstracted, Anat. Rec. **94**:487, 1946.

35. Gillman, J.; Gilbert, C.; Gillman, T., and Spence, I.: A Preliminary Report on Hydrocephalus, Spina Bifida and Other Congenital Anomalies in the Rat Produced by Trypan Blue, South African J. M. Sc. **13**:47-90, 1948.

36. Turner, W.: On Some Congenital Deformities of the Human Cranium, Edinburgh M. J. **11**:133-141, 1865.

37. O'Rahilly, R., and Twohig, M. J.: Foramina Parietalia Permagna, Am. J. Roentgenol. **67**:551-561, 1952.

38. Poirier, M., and Charpy, A.: Traité d'anatomie humaine, Paris, Masson & Cie: (*a*) Ed. 3, 1920, Vol. 2, Pt. 3; (*b*) Ed. 4, 1931, Vol. 1, Pt. 1.

39. Knott, J. F.: On the Cerebral Sinuses and Their Variations, J. Anat. Physiol. **16**:27-42, 1881.

orifice closed either externally or internally in 247 (48%) (LeDouble,[40] 1903); such a pit is more frequently present on the internal surface of the bone (Poirier and Charpy,[38] 1931) but was found by Boyd[41] (1930, 1934) in only 1.6% of 1,500 crania, "at or below the inion." The inioendinial canal is shown in Figure 2.

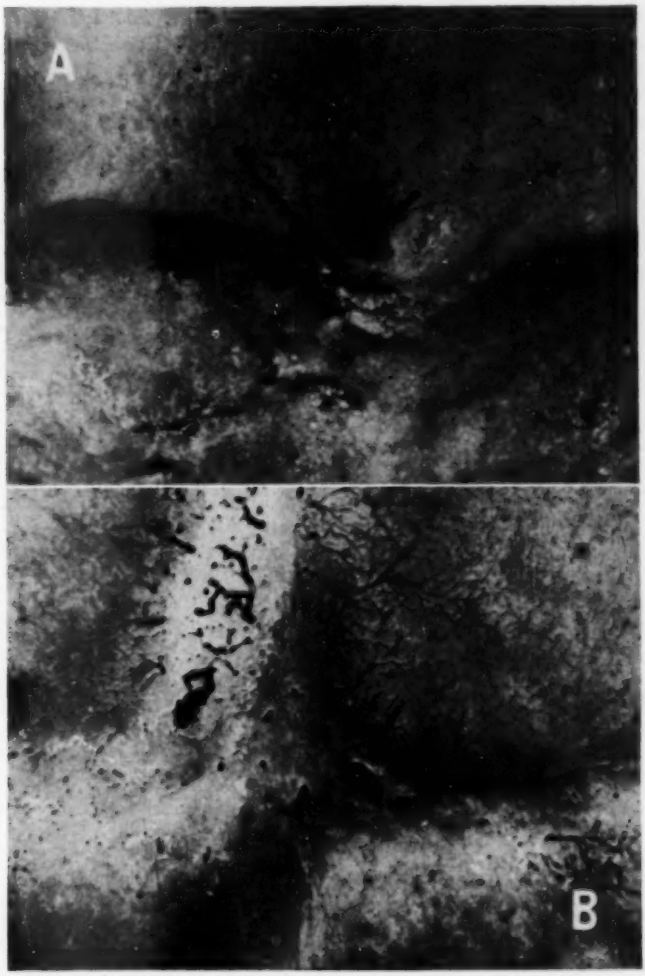

Fig. 2.—The inioendinial canal of a human skull: *A*, extracranial aspect. *B*, intracranial aspect.

40. LeDouble, A.: Traité des variations des os du crâne de l'homme, Paris, Vigot Frères, 1903.

41. Boyd, G. I.: (*a*) The Emissary Foramina of the Cranium in Man and the Anthropoids, J. Anat. **65**:108-121, 1930; (*b*) The Emissary Foramina of the Cranium in Primates, ibid. **69**:113-117, 1934.

It should be remembered that in examining dried skulls it is seldom possible to infer the formation of the confluence and transverse sinuses (Hayner,[42] 1949).

Reuben and Cleaver [43] (1913) described an oxycephalic head of a boy aged 7½ who showed marked dilatation of the veins of the face and neck. There was "a distinct opening in the skull beneath the external occipital protuberance; no encephalocele was present. This opening was probably of a compensatory nature." In discussing this case Boyd [44] (1930) refers to "a large occipital emissary vein," mention of which we have not observed in the original article.

Boyd [41b] (1934) noted that the human parietal foramen "varies in position within fairly well-defined limits," whereas in Primates in general it may be found

Fig. 3.—Part of the norma occipitalis of the skull of a siamang (Symphalangus syndactylus syndactylus). A lambdoid-sutural bone can be seen at the junction of the sagittal and lambdoid sutures. Just below the lambdoid-sutural bone a small median vascular canal (which extends through the thickness of the skull) can be identified in the apex of the occipital bone. (This specimen was lent to the author by Miss Barbara Lawrence, Department of Mammalogy, Harvard University Museum of Comparative Zoology [M.C.Z. 36032].)

"even in the apex of the occipital bone." He considered that foramina in the occipital apex "correspond" [45] to the human parietal foramina and he included them

42. Hayner, J. C.: Variations of the Torcular Herophili and Transverse Sinuses; abstracted, Anat. Rec. **103**:542, 1949.

43. Reuben, M. S., and Cleaver, E. E.: Oxycephaly, Arch. Pediat. **30**:820-824, 1913.

44. Boyd,[41a] p. 114. Boyden, A.: Homology and Analogy: A Critical Review of the Meanings and Implications of These Concepts in Biology, Am. Midland Naturalists **37**:648-669, 1947.

45. The concept of homology (see Boyden, A.: Homology and Analogy: A Critical Review of the Meanings and Implications of These Concepts in Biology, Am. Midland Naturalists **37**:648-669, 1947, for an excellent discussion), at all times difficult, is particularly so in the case of "negative" structures like foramina.

under the latter heading. A well-marked example of such an aperture (present both intracranially and extracranially) in a siamang is shown in Figure 3.

We may conclude that there is at present no evidence available by which to relate normal occipital openings to those associated with meningoceles or dermoid cysts.

DEVELOPMENT OF OCCIPITAL BONE

The following account of the development of the occipital bone is based on the studies of Lacoste [46] (1930). Arising in cartilage around the foramen magnum, the human occipital bone develops as an anteroinferior part (basioccipital; pars basilaris, B.R., B.N.A.), two lateral parts (exoccipital; pars condylaris, B.R.; pars lateralis, B.N.A.), and a posterosuperior part (supraoccipital; pars squamosa, B.R., inferior portion; squama occipitalis, B.N.A., inferior portion). A further

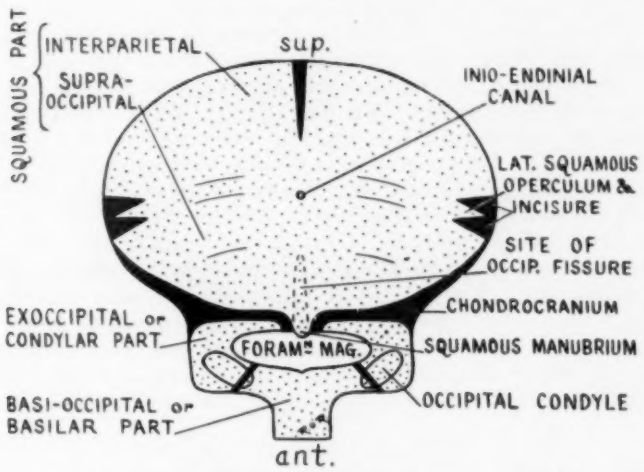

Fig. 4.—Scheme of the development of the human occipital bone.

part, between the supraoccipital part and the parietal bones (interparietal; pars squamosa, superior portion) develops in membrane. Ossicles in the region of the parieto-occipital suture may be called lambdoid-sutural bones (Jones,[47] 1949); a complicated nomenclature (preinterparietal, inca bone, etc.) has arisen around these highly variable ossicles. There appears to be considerable variation in occipital development in general, but in man (Fig. 4) there is a tendency for the supraoccipital part to ossify from one center and then fuse with two ill-separated interparietal centers which appear at a slightly later embryonic stage, about 40 mm. (approximately 9 weeks). Laterally at the line of fusion a lateral squamous incisura (fissura mendosa) remains for some time and may become divided into

46. Lacoste, A.: Sur le développement de l'écaille occipitale étudiée comparativement chez le mouton et chez l'homme, Arch. anat., histol. et embryol. **12**:1-47, 1930.

47. Jones, F. W.: In Buchanan's Manual of Anatomy, Ed. 8, London, Baillière, Tindall & Cox, 1949.

two chief parts (supraopercular and infraopercular) by an osseous prolongation (lateral squamous operculum).

The supraoccipital portion of the occipital bone is at first arranged around the dorsal part of the original foramen magnum and this part of the foramen is called the "occipital fissure." By a complex and variable process, the occipital fissure is obliterated, partly by apposition of its margins and partly by interposition of a median process of the supraoccipital portion (manubrium squamae occipitalis), which thus forms the dorsal border of the definitive foramen magnum. In rare cases the manubrium is an independent structure, called Kerckring's (1640-1693) ossicle.

Nothing appears to be recorded concerning the development of the inioendinial canal, but presumably it arises as a small vascular aperture at the junction of the interparietals and the supraoccipital.

From this summary of occipital embryology it can be seen that anomalous median occipital apertures are located (*a*) between the interparietals, (*b*) at the interparietal-supraoccipital junction, or (*c*) in the region of the occipital fissure. A defect in the interparietal region is rare, but, as has been mentioned already, such cases have been described. Girardier [2] (1939), who published an instance, stated that the high site is that occupied by Kerckring's ossicle and that this ossicle may possibly play a role in the production of meningoceles at this level. From the foregoing paragraphs it will be apparent that Girardier was in error concerning the location of Kerckring's bone. Most of the abnormal openings are situated lower down, however, and, regarding these, if it be held that pressure effects are of importance in the formation of cranial defects, the occipital fissure may be looked upon as a site of decreased resistance to pressure. (Perhaps, the extension of the defect in Figure 1 is the cranial end of the occipital fissure.) The admission of such a mechanical factor, however, would leave many other problems to be solved, such as the localized nature of the anomaly in so many instances. Oversimplification regarding teratogenesis should be avoided rigorously.

SUMMARY AND CONCLUSIONS

A case of occipital meningocele is illustrated. The patient was a boy aged 10 who had a median cranial defect below the inion.

A review of the literature on occipital meningo(encephalo)celes and dermoid cysts shows that the associated cranial defects occur (*a*) rarely above the occipital protuberances (even as high as the lambda), (*b*) sometimes at the protuberances, or (*c*) most commonly between the protuberances and the foramen magnum. The defect may extend into the foramen magnum and may be associated with cervical spina bifida. A case of occipital opening associated with craniolacunia is mentioned, and the association between meningocele in general and craniolacunia is noted.

Defective occiput and bifid vertebral arches are both median deficiencies in the dorsal wall of the neural axis. Recent writers on craniospinal defects stress the influence of cerebrospinal fluid disturbances, but some authors concede other modes of formation, also.

Anomalous occipital openings are generally associated with meningo(encephalo)-cele or dermoid cyst, whereas foramina parietalia permagna are closed by membrane and transmit merely some minute vessels. In the normal occipital bone there

is generally either an inioendinial canal (for the occipital emissary vein) or at least an internal or external vascular orifice. An opening near the apex of the occipital bone (which is believed by Boyd to "correspond" with the human parietal foramen) is sometimes encountered in Primate skulls, and a well-marked case is illustrated. There is no evidence available that anomalous occipital apertures are related to any of these normal openings.

The development of the human occipital bone (from basioccipital, exoccipital, and supraoccipital, and interparietal portions) is summarized. The relevant embryology suggests that anomalous median occipital apertures are located (*a*) between the interparietals, (*b*) at the interparietal-supraoccipital junction, or (*c*) most commonly in the region of the "occipital fissure." If it be held that pressure effects are of importance in the formation of cranial defects, then the "occipital fissure" may be regarded as a site of decreased resistance. The basis of such features as the localization of the defect remains entirely unknown.

EXPERIMENTAL CHOLESTEROL ATHEROSCLEROSIS

XI. Studies with Vitamin A

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AND
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NEW YORK

THE EFFECT of several vitamins on experimental cholesterol atherosclerosis in rabbits has already been reported. Thiamine hydrochloride and ascorbic acid administered intramuscularly [1] and d,l-α-tocopherol given orally [2] neither inhibited nor accentuated the deposition of cholesterol in the aorta of rabbits fed cholesterol. On the other hand, d,l-α-tocopherol injected intramuscularly increased the aorta cholesterol of cholesterol-fed rabbits.[3]

The present paper details the results obtained with the oral administration of vitamin A.

MATERIAL AND METHODS

Sixty-nine male rabbits, 3 to 5 months old, were used in this study. The experimental period extended for 14 weeks. All animals received a basic ration of rabbit chow [4] daily. Twenty-three rabbits served as a control group. Ten animals were fed 50,000 U. S. P. units of vitamin A,[5] added to the chow, three times weekly. Seventeen animals received 1 gm. of cholesterol, mixed with the food, three times weekly. Nineteen rabbits were fed 50,000 units of vitamin A and 1 gm. of cholesterol three times weekly. Care was taken to ensure that the vitamin A and the cholesterol were completely consumed by the animals.

The total cholesterol in whole blood (obtained from the ear) was determined by a modified Bloor [6] method at intervals of two weeks. At the end of the experimental period the rabbits were killed by an intracardiac injection of 20 ml. of air. The aorta was removed and its cholesterol content determined as previously described.[7] The blood removed for chemical analysis prior to killing the animals (14th week) was obtained by cardiac puncture. The cholesterol contents of these bloods were estimated by the Shoenheimer-Sperry [8] method and the lipid phosphorus by a modified Whitehorn [9] procedure.

From the Department of Medicine, New York University Post-Graduate Medical School.

1. Flexner, J.; Bruger, M., and Wright, I. S.: Arch. Path. **31**:82, 1941.
2. Dam, H.: J. Nutrition **28**:289, 1944.
3. Bruger, M.: Proc. Soc. Exper. Biol. & Med. **59**:56, 1945.
4. This product is prepared by the Ralston Purina Company, St. Louis, and contains a mixture of grains and alfalfa hay. It is said to contain 23 parts per million of carotene but no vitamin A.
5. The vitamin A was supplied by E. R. Squibb & Sons, through the kindness of Dr. H. Sidney Newcomer. This vitamin was in the natural (ester) form obtained by distillation and diluted with corn oil.
6. Sackett, G. E.: J. Biol. Chem. **64**:203, 1925.
7. Bruger, M., and Fitz, F.: Arch. Path. **25**:637, 1938.
8. Sloenheimer, R., and Sperry, W. M.: J. Biol. Chem. **106**:745, 1934.
9. Whitehorn, J. C.: J. Biol. Chem. **62**:133, 1924.

The procedure of Whitehorn was modified as follows: The dried lipoid material was digested slowly in a sand bath. This step was introduced so that several determinations could be carried out at the same time. The conversion of carbon to carbon dioxide was hastened by adding 1 to 2 drops of 30% hydrogen peroxide and passing the tube several times through an open flame. The 10-minute digestion period following the appearance of white fumes was thereby eliminated. A freshly prepared solution of hydroquinone was used in preference to the preserved solution mentioned by Whitehorn. The Coleman Junior Spectrophotometer was employed. The per-cent transmittance was measured at wave length 700 μ, a reagent blank being used as a reference. Cuvettes 6-310 were used. The reagent blank consisted of 1 ml. of concentrated sulfuric acid, 2 ml. of 20% sodium sulfite, and 5 ml. of water. This mixture was treated in the same manner as the unknown from the beginning of the postdigestion period. The color-development phase was read at a dilution of 20 ml. The per-cent transmittance of the unknown was compared with a previously calibrated curve ranging from 0.01 to 0.05 mg. of phosphorus. Normal values fall in this range if a mixture of serum with alcohol-ether in the ratio of 3 to 50 is used. Five milliliters of a filtrate from this mixture was used for each determination. For values outside the normal range, the amount of filtrate used in the determination was altered so that the quantity measured fell within the 0.01-to-0.05-mg. range.

TABLE 1.—*Average Concentrations of Whole-Blood Cholesterol and Aorta Cholesterol in Control and Experimental Rabbits*

Experiment	Animals	Average Concentrations of Whole-Blood Cholesterol, Mg. per 100 Cc.								Average Concentration of Aorta Cholesterol, Mg. per 100 Gm. Dry Aorta
		0	2	4	6	8	10	12	14	
Control	3	149	48	69	79	81	67	155	153	300
Vitamin A feeding	10	59	61	72	80	115	93	106	106	350
Cholesterol feeding	17	78	164	225	309	317	370	597	540	1,546
Cholesterol + vitamin A feeding	19	83	116	170	275	421	337	474	386	1,443

TABLE 2.—*Average Terminal Concentrations of Serum Cholesterol and Serum Lipid Phosphorus, and the Phospholipid Cholesterol Ratios, in Control and Experimental Rabbits*

Experiment	Animals	Serum Cholesterol, Mg. per 100 Cc.	Serum Lipid Phosphorus, Mg. per 100 Cc.	Serum Phospholipid (Calculated), Mg. per 100 Cc.	Ratio of Phospholipid to Total Cholesterol
Control	20	68	3.8	95.0	1.40
Vitamin A feeding	6	76	4.1	102.5	1.30
Cholesterol feeding	8	697	11.4	285.0	0.41
Cholesterol + vitamin A feeding	8	617	11.8	295.0	0.48

The ratio of phospholipids to total cholesterol was calculated from the formula

$$\frac{\text{Lipid phosphorus (mg./100 cc.)} \times 25}{\text{Total cholesterol (mg./100 cc)}}$$

RESULTS

Table 1 gives the average concentrations of the total cholesterol of whole blood obtained at intervals of two weeks and the terminal concentration of aorta cholesterol for the four groups of rabbits. It may be seen that the ingestion of vitamin A did not influence the whole blood and aorta cholesterol of rabbits fed a basic ration of chow. In rabbits fed cholesterol, the addition of this vitamin to the food did not significantly inhibit or augment the hypercholesteremia or modify the deposition of cholesterol in the aorta.

Table 2 gives the average terminal concentrations of serum cholesterol and serum lipid phosphorus, and the phospholipid/cholesterol ratios, for the four groups of rabbits. The average ratio in normal rabbits was 1.4. It was not altered significantly by adding vitamin A to the diet. In the rabbits fed cholesterol the phospholipid/cholesterol ratio was decreased to 0.41. This represents a considerably greater increase of serum cholesterol as compared with serum lipid phosphorus. The feeding of vitamin A to cholesterol-fed rabbits failed to modify significantly the decreased ratio obtained by the feeding of cholesterol alone.

CONCLUSIONS

Vitamin A administered orally did not affect the cholesterol content of the blood or that of the aorta in normal rabbits. It did not modify the increased cholesterol content of the blood and the aorta in cholesterol-fed rabbits. The decrease of the ratio of serum phospholipids to total cholesterol in rabbits fed cholesterol was not altered by the simultaneous addition of vitamin A.

ABDOMINAL GAS CYSTS (PNEUMATOSIS CYSTOIDES INTESTINORUM HOMINIS)

An Analysis with a Report of a Case and a Critical Review of the Literature

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THE DISEASE characterized by the presence of multiple, gas-filled, sessile or pedunculated cysts involving portions of the gastrointestinal tract and occasionally other organs of the abdominal cavity is known by the name of pneumatosis cystoides intestinorum hominis or abdominal gas cysts.[1] A disease with identical morphological features occurs also in hogs [2] and, rarely, in other animals.[3] In man the entity is undoubtedly of rare occurrence. In this country and in Canada, relatively few authenticated cases have been reported.[4]

Although several extensive reviews of the subject have appeared,[5] only few of the available textbooks mention the entity.[6]

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1. In the present paper the terms "pneumatosis cystoides intestinorum" and "intestinal" or "abdominal gas cysts" will be used interchangeably.

2. (*a*) Mayer, J.: Hufelands J. prakt. Arzneikunde u. Wundarzneikunde **61**:67, 1825. (*b*) Jaeger, A.: Verhandl. deutsch. Gesellsch. path. Anat. **10**:251, 1906. (*c*) Cadéac, M. C.: J. méd. vét. et de zootech. Lyon **13**:416, 1909, cited by Biester and others. (*d*) Joest, E.: Spezielle pathologische Anatomie der Haustiere, Ed. 2, Berlin, 1926, Vol. 1, pp. 571-576. (*e*) Naeslund, J.: Zur Kenntnis der Pneumatosis cystoides intestinorum: Pathologisch-anatomische und experimentelle Studien, Thesis (Upsala), Stockholm, Isaac Markus, 1924.

3. (*a*) Hey, R.: Deutsche Ztschr. Chir. **154**:250, 1920 (chicken). (*b*) Mills, H. W.: Surg., Gynec. & Obst. **40**:387, 1925 (sheep). (*c*) Naeslund [2e] (sheep and chicken).

4. (*a*) Finney, J. M. T.: J. A. M. A. **51**:1291 (Oct. 17) 1908. (*b*) Turnure, P. R.: Ann. Surg. **57**:811, 1913. (*c*) Sloan, H. G.: Surg., Gynec. & Obst. **30**:389, 1920. (*d*) Twyman, E. D.: J. A. M. A. **73**:1840 (Dec. 13) 1919. (*e*) Bubis, J. L., and Swanbeck, C. E.: Ann. Surg. **75**:620, 1922. (*f*) Mills.[3b] (*g*) Moore, R. A.: Am. J. Dis. Child. **38**:818 (Oct.) 1929. (*h*) Jackson, J. A.: Surg., Gynec. & Obst. **71**:675, 1940. (*i*) Lerner, H. H., and Gazin, A. I.: Am. J. Roentgenol. **56**:464, 1946. (*j*) Parson, R. M., and Parson, W. B.: Canad. M. A. J. **58**:71, 1948. (*k*) Gazin, A. I.; Brooke, W. S.; Lerner, H. H., and Price, P. B.: Am. J. Surg. **77**:563, 1949. (*l*) Morgan, H. W., and Barg, E. H.: M. Radio. & Photog. **26**:128, 1950. (*m*) Freedlander, S. O., and Teitelbaum, S. S.: West. J. Surg. **58**:192, 1950. (*n*) Dale, W. A., and Pearse, H. E.: Surg., Gynec. & Obst. **90**:215, 1950. (*o*) Schorr, S.; Ullmann, T. D., and Laufer, S.: A. M. A. Arch. Int. Med. **88**:362 (Sept.) 1951. (*p*) Creese, P. G.: Gastroenterology **19**:75, 1951.

5. (*a*) Arzt, L.: Frankfurt. Ztschr. Path. **6**:85, 1910. (*b*) Turnure,[4b] (*c*) Nitch, C. A. R., and Shattock, S. G.: Section of Pathology, Proc. Roy. Soc. Med. **12**:46 (Pt. 3) 1919. (*d*) Letulle, M.: Bull. Acad. méd. **36**:315, 1919. (*e*) Naeslund.[2e] (*f*) Lecoeur, P. M.: La pneumatose kystique de l'intestin et sa pathogénie, Thesis, Paris, Legrand, 1924. (*g*) Kopelowitz, M.: Arch. path. Anat. **248**:369, 1924. (*h*) Mills.[3b] (*i*) Leo, C.: Arch. ital. chir. **16**:373, 1926. (*j*) Reichel, P., and Staemmler, M.: Neue deutsche Chir. **33B**:88, 1933. (*k*) Ferrandu, S.: Arch. sc. med. **60**:493, 1935. (*l*) Kilian, H.: Neue deutsche Chir. **60**:277, 1939. (*m*) Sauser-Hall, P.: Gastroenterologia **65**:193 and 313, 1940. (*n*) Vaz, O.: Rev. méd. mun. Rio de Janeiro **2**:449, 1941. (*o*) Llorena, D. J., and Huerta, M. H.: Rev. clín. españ. **12**:391, 1944.

(Footnotes continued on next page)

It appears therefore useful to report a classic case of pneumatosis cystoides intestinorum (or intestinalis) and to review the literature, with emphasis on the natural history of the disease and its diagnosis and prognosis, since there is little available information on these aspects of gas cysts.

REPORT OF CASE

A 59-year-old white man was admitted to Kings County Hospital on April 4, 1950. The chief complaint was inability to hold down any food, a difficulty which had been present for four or five days. Two days prior to admission the patient experienced a sudden onset of abdominal pain which was severe enough to put him to bed. The pain had persisted without change and was accompanied by constant nausea. There had been several bowel movements since the onset of the illness. No fresh or old blood was found in the stools. The patient gave a history of a gastric ulcer of 19 years' duration. For several years he had been able to take only small feedings. Recently he noticed weakness and loss of weight, although there was no anorexia.

On admission his temperature was 100 F., pulse rate 92, and respiration rate 32. The blood pressure was unobtainable. The patient was an extremely dehydrated, thin, and wasted white man in severe distress. The only positive findings on physical examination were abdominal epigastric distention and tympanites. There was tenderness in the right upper abdominal quadrant. The liver and the spleen were not palpable. The impression was pyloric obstruction due to chronic peptic ulcer.

No urine was obtained on catheterization of the bladder. The hemoglobin was 13 gm. per 100 cc. (Sahli). The total leucocyte count was 12,400. Gastric suction yielded 500 cc. of dishwater-colored fluid.

The CO_2-combining power was 61%. A blood urea determination showed 78 mg. per 100 cc. Gastric analysis revealed an absence of free hydrochloric acid, low total acidity, and presence of blood in the specimen.

The original report on the x-ray studies of the thorax and the abdomen (flat plates) stated that these showed an interposition of bowel between the liver and the right leaf of the diaphragm, numerous fluid levels, and no pleural or pulmonary abnormalities.

After necropsy, the following interpretation of the plates was made: "Chest: No evidence of pleural or pulmonary pathology. The thoracic cage appears normal and presents no abnormalities. The diaphragmatic domes are normal in position and contour. Multiple areas of cyst-like or bleb formations are noted beneath the right diaphragmatic dome. Few small gas-containing areas assume a ring and double-ring-like configuration, displacing the liver inferiorly and medially. Multiple fluid levels are noted within the large and the small bowel.

"Examination of the abdomen reveals the formerly noted abnormalities beneath the right diaphragmatic dome" (Fig. 1).

In spite of supportive therapy, the patient died three days after admission, before any operative procedure could be attempted. The autopsy (No. 25021) was performed the same day by Dr. John M. Lukeman.

Necropsy.—On external examination of the body a few ecchymoses were noted. The thoracic and pleural cavities were normal. The heart and the lungs showed no pathological changes of significance. The capsule of the spleen was slightly thickened, but the organ itself was apparently normal. The liver was soft and congested. A few

6. (*a*) Siegmund, H., in Handbuch der speziellen pathologischen Anatomie und Histologie, edited by F. Henke and O. Lubarsch, Berlin, Springer-Verlag, 1929, Vol. 4, Pt. 3, pp. 405-409. (*b*) Kaufmann, E.: Lehrbuch der speziellen pathologischen Anatomie für Studierende und Ärzte, Ed. 10, Berlin, W. de Gruyter & Co., 1931, p. 713. (*c*) Bockus, H. L.: Gastro-Enterology, Philadelphia, W. B. Saunders Company, 1944, Vol. 2, pp. 131-132. (*d*) Illingworth, C. F. W., and Dick, B. M.: A Textbook of Surgical Pathology, Ed. 5, London, J. & A. Churchill, Ltd., 1945, pp. 499-500. (*e*) Moore, R. A.: A Textbook of Pathology, Ed. 2, Philadelphia, W. B. Saunders Company, 1951, p. 292.

small hemangiomas were present on cut section. The gall bladder, the pancreas, and the adrenal glands were not remarkable. The genitourinary tract did not reveal any abnormalities on gross examination.

The stomach was impressively distended. It contained approximately 2,000 cc. of foul-smelling fluid. In the pyloric area there was a small ulcer surrounded by a

Fig. 1.—X-ray plate showing the liver separated from the right leaf of the diaphragm. The space thus formed is filled with foamy, reticulated structures, some strongly suggestive of round cysts.

zone of prominent fibrosis, causing almost complete stenosis of the pylorus. The remainder of the gastric mucosa was hypertrophied. The duodenum and the ampulla of Vater were not remarkable. In the intestine, at a distance of approximately 15 ft. (4.5 meters) from the pylorus, a segment of the ileum was covered with clusters of cysts. The diseased portion measured approximately 6 ft. (about 2 meters) in length. The clusters covered fairly densely the serosal surface of the bowel (Figs. 2 and

3).[7] Several loops of the ileum were bound together by adhesions containing cysts (Fig. 4). One markedly congested loop of the intestine, covered with cysts, was twisted upon itself. In addition, this loop was compressed at its base by adhesions. The bowel above this area was obviously distended. The clusters of cysts measured up to 1 by 2 by 2 cm. They consisted of thin-walled bluish cysts with diameters varying from 1 to 10 mm., the majority averaging 4 to 5 mm. The cysts could be broken with ease, and were found to be smooth-walled and free of fluid. On section the cysts were seen mainly in the serosa of the bowel. Cross section of the clusters resembled honeycombs consisting of various-sized chambers. Cross sections of the adhesions showed the presence of densely packed cysts. One cyst measuring 3.5 cm. in diameter was found in the serosa of the distal portion of the cecum. The mucosa of the involved segment of the bowel appeared grossly intact except within

Fig. 2.—Portion of ileum (formalin-fixed) with clusters of cysts over serosal surfaces.

the obstructed loop, where it was hemorrhagic. The remaining portions of the intestine appeared grossly normal.

Microscopic Examination.—(*a*) Stomach: Sections of the pyloric area reveal a mucosal defect extending into the muscularis, measuring approximately 1 cm. in diameter. The edges of the ulcer are somewhat undermined. The base of the ulcer is covered by a layer of granulation tissue. Islets of preserved submucosa are present within the crater, but most of the submucosa is destroyed. Considerable thickening and fibrosis of the stomach wall are noted in the area of the ulcer. Sections of other portions of the stomach reveal normal mucosa arranged in exaggerated folds.

7. Dr. Joseph Ehrlich, Pathologist at Lebanon Hospital, Bronx, N. Y., gave me permission to examine a specimen of intestinal pneumatosis and utilize a photograph of it, as shown in Figure 3.

(*b*) Ileum: Sections of the intestinal wall within the zone of obstruction reveal an area of early necrosis, sharply demarcated and confined to the mucosa. There is also a polymorphonuclear infiltration around and in the zone of necrosis. The serosa at the same level is thickened, edematous, and infiltrated by inflammatory cells.

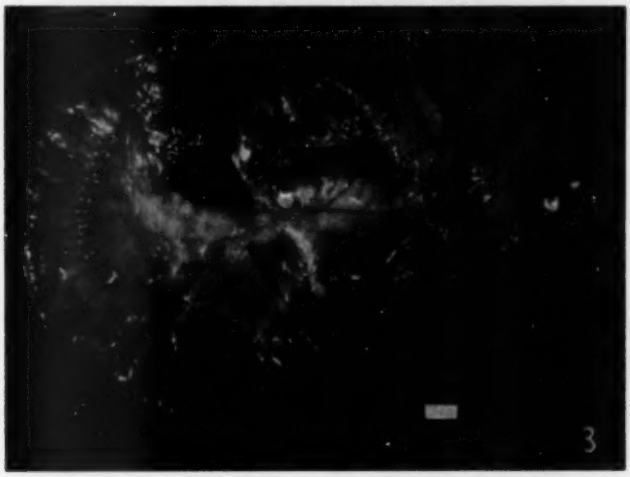


Fig. 3.—Photograph by courtesy of Dr. Joseph Ehrlich, Lebanon Hospital, Bronx, N. Y. The patient, a white man 50 years of age, had a gastrectomy performed for pyloric obstruction of 15 years' duration. As an accidental finding, pneumatosis cystoides, involving a loop of small bowel was found. The photograph shows a resected loop of bowel with clusters of cysts over the serosa.

Fig. 4.—Cross section of adjacent loops of intestine showing adhesions containing cysts.

Multiple and serial histological sections of the area of intestine showing the cystic changes fail to disclose any disruption of the continuity of the mucosa. The deeper layers of the mucosa are moderately infiltrated with lymphocytes, plasmacytes, and eosinophilic leucocytes. The wall of the intestine appears thickened by the presence of innumerable cystic spaces, most of which are located within the

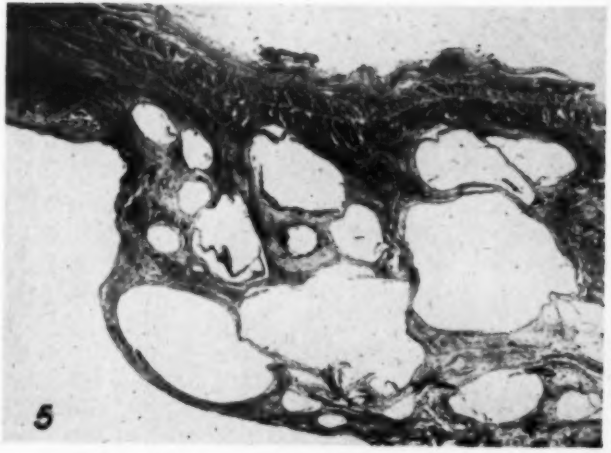


Fig. 5.—Wall of ileum with a cluster of cysts accounting for a conspicuously thickened serosa. Hematoxylin and eosin stain; × 7.5.
Fig. 6.—Cyst lined by simple endothelial cells and flattened giant cells. Hematoxylin and eosin stain; × 7.5.

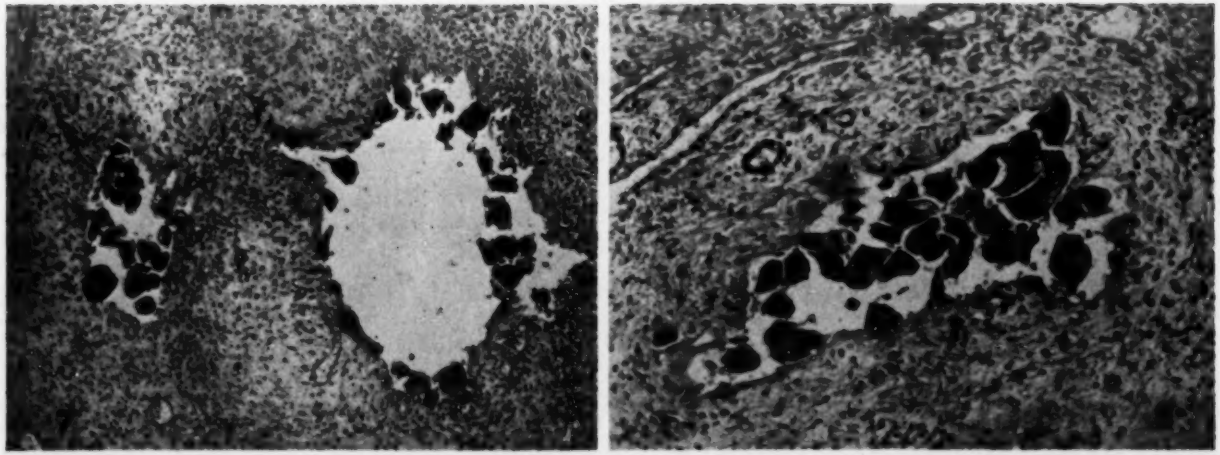
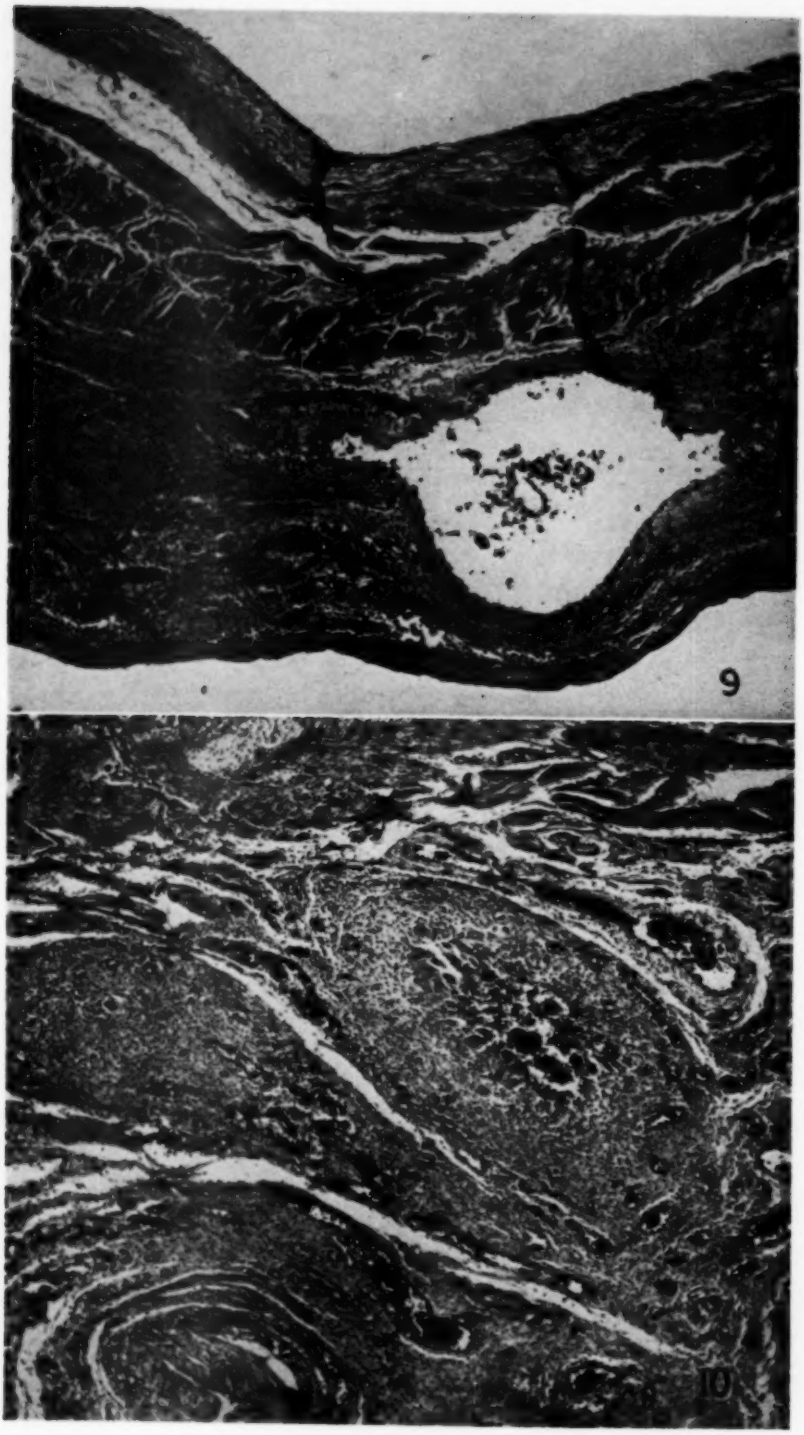


Fig. 7.—Giant cells sloughing off the cyst lining. The smaller cyst contains many giant cells lying free in the lumen. There is a moderate inflammatory reaction of the stroma. Hematoxylin and eosin stain; ×75.

Fig. 8.—Higher power of a small cystic space filled with giant cells. Note that the space is practically bare of any lining. The surrounding connective tissue is free of inflammatory cells. Hematoxylin and eosin stain; × 140.



Figures 9 and 10

(See legends on opposite page)

subserosa (Fig. 5). The cysts are rare within the submucosa and muscularis. The cysts occur singly and in clusters. In clusters, the cysts are separated from each other by thin bands of hyaline connective tissue sparsely infiltrated by mononuclear cells with a predominance of lymphocytes and a scattering of polymorphonuclear leucocytes and large cells of histiocytic variety. The cysts are partly lined by a single layer of cells, which are either flattened and elongated or cuboidal to columnar in shape. These cells possess a deeply eosinophilic cytoplasm and small dark nuclei. Other portions of the cysts are lined by flattened multinucleated giant cells, containing from 10 to 50 nuclei or more (Fig. 6). The cytoplasm of the giant cells is eosinophilic. Mitotic figures are occasionally observed within the endothelial lining cells. In a few of the smaller cysts there is an increasing abundance of giant cells, which appear to slough off the cyst wall and lie free within the lumen of the cyst (Fig. 7). In many cysts the wall thus becomes free of cellular lining, with only a rare flattened endothelial-like cell or giant cell still attached to the wall. Indeed, one finds smaller, slit-like cystic structures filled with masses of huge giant cells. These structures are surrounded by dense hyaline fibrous tissue, which is free of inflammatory cells (Fig. 8).

In some areas of the serosa the inflammatory reaction is more intense. There the serosa is thickened, somewhat edematous, and densely infiltrated with inflammatory cells. Both eosinophilic polymorphonuclear leucocytes and histiocytes are quite numerous. The histiocytic elements become occasionally elongated, acquire a more eosinophilic tinge, and resemble epithelioid cells. Within these areas of inflammation one sees small spaces containing one or two giant cells of the previously described type. A few larger cysts, in the same area, are surrounded by connective tissue showing considerable inflammatory reaction (Fig. 9).

In still different areas one can see granulomas composed of large mononuclear cells, resembling epithelioid cells, together with an abundant admixture of eosinophilic polymorphonuclear leucocytes (Fig. 10). The centers of these granulomas contain spaces filled with giant cells.

Submucous cysts, resembling the subserosal cysts, are rare. The diameter varies from a few millimeters to a centimeter. The larger cysts tend to elevate the mucosa. Occasionally, a submucosal or, more frequently, a subserosal cyst compresses the adjacent layer of muscle. Only a rare intramuscular cyst is noted. It is then distinctly separated from the surrounding muscle by a thin wall of connective tissue. Cysts of identical morphological characteristics are also found within the fibrous adhesions binding the loop of bowel. The cysts bind one loop of bowel to the other without any transition and are surrounded by bands of fibrous connective tissue (Fig. 11).

The blood vessels are not unusual except for some hyperemia in the areas of active serosal inflammation and around the granulomas. In one area there is a group

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EXPLANATION OF FIGURES 9 AND 10

Fig. 9.—Severe inflammatory reaction in the serosa of the bowel. Hematoxylin and eosin stain; × 75.

Fig. 10.—Two well-formed granulomas containing giant cells in the center. Hematoxylin and eosin stain; × 55.

of dilated vessels lined by a layer of flat cells. These vessels contain no cells and appear to be lymphatics. In the vicinity of these vessels there are numerous cysts of all descriptions. On serial sections no definite transition between a cyst and a lymphatic vessel could be demonstrated.

Special stains, including Goldner's modification of Masson's trichrome stain, Wilder's reticulum stain, Mallory's phosphotungstic acid-hematoxylin stain, Weigert-Gram stain, and the Ziehl-Neelsen method for acid-fast organisms have not contributed to a better understanding of the lesions. No micro-organisms have been found within the cysts and tissues. Fat stains have revealed no lipoids within the cysts or the cyst lining.

(*c*) Other Organs: The microscopic findings in other organs were irrelevant.

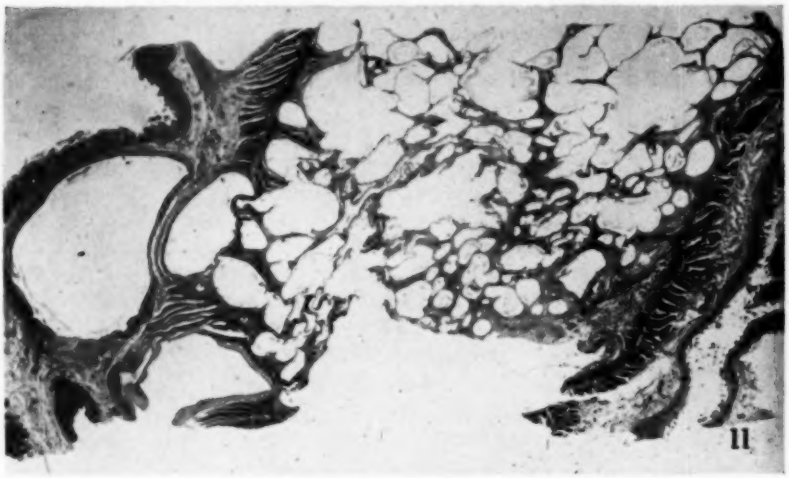

Fig. 11.—Low power magnification of adhesions between two loops of bowel. Note the presence of cysts; a large submucous cyst lifting the mucosa is also visible on the photograph. Masson's trichrome stain; × 7.5.

Diagnosis.—The final anatomical diagnosis was established as follows:

Primary: pyloric peptic ulcer, chronic, with fibrosis of the wall and pyloric stenosis; gas cysts of the intestine (pneumatosis cystoides intestinorum) involving the ileum and cecum; fibrous and cystic adhesions of the ileum; intestinal obstruction due to adhesions and volvulus; necrosis of mucosa of the obstructed loop of intestine.

Secondary: apical scar; interstitial pulmonary fibrosis; focal atelectasis and emphysema; chronic bronchitis, mild; fatty degeneration of liver cells; cavernous hemangioma of the liver; fibrosis of the spleen; fibrosis and fatty infiltration of the pancreas; vacuolar degeneration and focal lymphocytic infiltration of the adrenal; mild arterial nephrosclerosis; senile keratosis of the skin of the thighs; early adenocarcinoma of the prostate.

Cause of Death: gas cysts of intestine; intestinal adhesions; intestinal obstruction.

REVIEW OF THE LITERATURE

One hundred ninety-four papers describing 255 cases of the disease were reviewed.[8] Four additional communications containing reports of six cases were rejected because of incompleteness.[9] Six papers discussing 31 cases of the disease in infants and small children will be discussed separately. Out of the remaining 225 cases, 9 were found to be repetitions of cases already included.[10] Three cases were rejected for reasons given in the chapter on differential diagnosis. This leaves 213 cases, including the present one, to be analyzed below.

EARLIEST RECORDS OF THE DISEASE

The English authors ascribe the first, although inadequate, description of abdominal gas cysts observed in humans to John Hunter (1728-1793). The museum of the Royal College of Surgeons contains two old specimens of pneumatosis cystoides intestinorum, one of which was apparently contributed by Jenner.[11]

The French authors claim that the first description of the disease is that by Duvernoy.[12]

It is reported that this disease in hogs had been known to butchers for a long time prior to the first adequate description by Mayer,[2a] who first coined the name "pneumatosis cystoides intestinorum." The first satisfactory and well-documented description of the human disease is that by Bang.[13] Thirteen years after Bang's paper, Hahn [14] recognized the morphological similarity between the disease in hogs and that in humans and applied the name "pneumatosis cystoides intestinorum" to the human disease. Hahn's observation was also the first one on a living patient, although Nigrisoli [15] had apparently observed a case a year before.

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8. Some of the older papers quoted were inaccessible for personal inspection. They have been utilized only when extensive quotations were found, preferably in more than one apparently reliable source.

In spite of all efforts toward completeness, the present review certainly does not include all the publications on the subject.

9. (*a*) Lubarsch, O.: Verhandl. deutsch. Gesellsch. path. Anat. **10**:251, 1906 (three cases in discussion of Jaeger's paper [2b]). (*b*) Herman: Sprawozd. z pos. sekcyi przemyskiej Tow. Lek. galic. **8**:118, 1908, cited by Brückner, S.: Polska gaz. lek. **10**:520, 1931. (*c*) Uchino, K., cited by Mills.[3b] (*d*) Ciuto, G., cited by Mills.[2b]

10. (*a*) Nowicki, W.: Arch. path. Anat. **198**:143, 1909, Case 3, same as Kucera's (cited by Ferrandu [5k]). (*b*) Lindström, I.: Allm. sven. Läkartidn. **9**:345, 1912, and Naeslund's [2e] Case 3. (*c*) Jaboulay: Lyon méd. **96**:753, 1901, and Tolot's case, ibid. **96**:955, 1901. (*d*) Ciechanowski, S.: Wien. med. Wchnschr. **50**:24, 1904; Arch. path. Anat. **203**:170, 1911 (Case 1). (*e*) Letulle [5d] and Weil, M. P.: Ann. méd. **8**:11, 1920. (*f*) Moulonguet, M. P.: Bull. et mém. Soc. nat. chir. Paris **57**:571, 1931, and case observed by M. J. Hertz (no paper). (*g*) Nitch and Shattock.[5c] Nitch, C. A. R.: Brit. J. Surg. **11**:714, 1923-1924 (two cases). (*h*) Apparently the same case was briefly described by A. Druckmann and S. Schorr (Acta med. orient. **6**:56, 1947) and then reported in considerable detail by Schorr, Ullmann, and Laufer.[4o]

11. Jenner, cited by Nitch and Shattock,[5c] and by Lamont, D.: Tr. Roy. Med.-Chir. Soc. Glasgow **23**:113, 1929.

12. Duvernoy's case in Combalusier: Pneumopathologie ou traité des maladies venteuses, Paris, 1754, Vol. 1, p. 19, cited by Sauser-Hall.[5m]

13. Bang, B. L. F.: Nord. med. ark. (No. 18) **8**:1, 1876.

14. Hahn, E.: Deutsche med. Wchnschr. **25**:657, 1899.

15. Nigrisoli: Nuovo raccoglitore medico, September, 1902; cited by Turnure [4b] and Naeslund.[2e]

AGE AND SEX DISTRIBUTION OF THE DISEASE

Table 1 shows the age and sex distribution of the disease. It will be noted that the disease occurs considerably more frequently in males than in females, the ratio being approximately 3.5: 1. The peak of occurrence is between 30 and 50 years of age in males, and in the sixth decade in females.

GROSS AND MICROSCOPIC APPEARANCE OF CYSTS

Gas cysts of the intestine can be divided into two groups according to their appearance on gross examination. In the first group, of which our case is an excellent example, the gas cysts are visible over the serosal surface of the bowel, occurring singly and in clusters. They may be sessile or pedunculated and may vary

TABLE 1.—*Age and Sex Distribution*

Age, Yr.	2-10	11-20	21-30	31-40	41-50	51-60	Above 60	Unknown	Total
Male	3	5	30	40	41	16	8	4	147
Female	0	5	8	7	8	10	5	2	45
Sex unknown	..	..	..	1	..	..	..	20	21
Total									213

TABLE 2.—*Diseases Associated with Gas Cysts*

	Cases	
	No.	%
Lesions of Pyloric Area		
1. Gastric or duodenal ulcer, mostly with pyloric stenosis	117	55
2. Carcinoma of the stomach	7	3.3
Other Associated Lesions		
3. Intestinal tuberculosis	7	3.3
4. Acute and chronic appendicitis	4	2
5. Various lesions *	24	11.2
6. No disease ("primary")	33	15.4
7. Unknown	21	9.8
Total	213	100.0

* See text.

in size from a fraction of a millimeter in diameter to several centimeters. The clusters of cysts or conglomerates may become quite large, the one described by Lindström [16b] being the size of a child's head. The cysts involving the bowel surface have been variously compared to soap bubbles, hydatidiform mole, hydatid cysts, lymphangiomas, etc., according to their gross appearance.

In the second group the cysts are located within the submucosa only and are usually not visible on external examination. On palpation the involved segment of bowel has a spongy, cushion-like consistency. On section the resemblance of the cystic portions of bowel to honeycomb has been frequently evoked.

In both groups the cysts are thin-walled, contain gas, and under pressure break like balloons. The gas usually does not travel from one cyst to another, although there are exceptions to this.[16] In view of the large number of cases in which spon-

16. (*a*) Tung, P. C., and Ngai, S. K.: Chinese M. J. **47**:1, 1933. (*b*) Raffaelli, A.: Minerva chir. **4**:102, 1949. (*c*) Baetzner: Zentralbl. Chir. **51**:743, 1924.

taneous pneumoperitoneum has been reported in conjunction with pneumatosis cystoides intestinalis, it is probable that the cysts can rupture spontaneously. Adhesions, which sometimes contain cysts, have been observed between the affected loops of bowel.

In the great majority of cases gas cysts are associated with another lesion of the gastrointestinal tract. Table 2 gives the statistics relative to the associated diseases. Fifty-eight per cent of cases show lesions of the pyloric area, primarily of a stenotic type. Among those, the gastric ulcer predominates, whereas carcinoma of the stomach is infrequent, with only seven cases reported.[17] An equal number of cases of tuberculous enteritis[18] and four cases of appendicitis[19] are on record. Among other lesions found in conjunction with pneumatosis are acute and chronic enteritis,[20] chronic colitis,[21] gastroptosis,[22] gastric dilatation,[23] adhesive bands,[24] intestinal obstruction due to a bile stone,[25] diaphragmatic hernia,[26] stenosis of the esophagus secondary to ingestion of lye,[27] isolated nonspecific ulcerations of bowel,[28] intestinal parasites,[29] acute peritonitis,[30] and a previous end-to-end anas-

17. (*a*) Finney.[4a] (*b*) Bindi, F.: Riforma med. **18**:397, 1912. (*c*) Myassnikoff, V. K.: Sibirsk. Vrach. Gaz. Irkutsk **6**:86, 1913; abstracted, Zentralbl. Chir. **40**:507, 1913. (*d*) Matronola, G.: Policlinico (sez. chir.) **29**:610, 1922 (Case 2). (*e*) Naeslund,[2e] Case 2. (*f*) Ruckensteiner, E., and Kux, E.: Fortschr. Geb. Röntgenstrahlen **47**:661, 1933 (Case 2). (*g*) Dale and Pearse.[4n]

18. (*a*) Letulle, M.: Bull. Soc. Anat. Paris, cited by Letulle.[5d] (*b*) Pelnar, M.: Rozpr. českí Akad. cis Františka Josefa [etc.] v Praze **9**:12, 1900. (*c*) Lubarsch, O.: Arb. a. d. path. anat. Abt. d. k. hyg. Inst. zu Posen, 1901, p. 47; cited by Naeslund[2e] and Kopelowitz.[5g] (*d*) Verebélyi, T.: Wien. med. Wchnschr. **47**:2218, 1901. (*e*) Sauser-Hall,[5m] Cases 1 and 3. (*f*) Gerundo, M., and Chang, M. L.: Hawaii M. J. **8**:273, 1949.

19. (*a*) Woltmann, A. N.: Prakt. vrach., St. Petersburg **8**: 1909; abstracted, Zentralbl. Chir. **36**:616, 1909. (*b*) Philip, E.: Ein Fall von Pneumatosis intestinalis bei Appendicitis, Thesis, Leipzig, E. Lehmann, 1911. (*c*) Mills,[3b] Case 2. (*d*) Chazaro, E. P.: Gac. méd. México **73**:370, 1943.

20. (*a*) Nowicki,[10a] Cases 1 and 2. (*b*) Ruckensteiner and Kux,[17f] Case 3.

21. Bettoni, I.: Osp. maggiore **15**:155, 1927.

22. Ribeiro, E. R.: Bol. assist. méd. indig. Luanda **10**:5, 1939; cited by Vaz.[5n]

23. (*a*) Cristol and Porte: Presse méd. **27**:726, 1919. (*b*) Coelho, N. A.: An. Fac. med. Univ. São Paulo **15**:201, 1939 (Case 3). (*c*) Frostberg, N.: Acta radiol. **29**:521, 1948. (*d*) Miranda, M. P.; Monteiro, D., and de Carvalho, M.: Arq. clín. **6**:239, 1948.

24. (*a*) Steindl, H.: Deutsche Ztschr. Chir. **163**:44, 1921. (*b*) Onaca, N., and Kovacs, I.: Zentralbl. Chir. **63**:1398, 1936.

25. Drew, D.: Brit. J. Surg. **12**:803, 1924-1925.

26. Xanthopulides, A.: Iatrike **2**:Nos. 11 and 12, 1924; abstracted, Zentralbl. org. Chir. **32**:468, 1925 (Case 1).

27. Dressler, M.: Schweiz. med. Wchnschr. **1**:382, 1939; Helvet. med. acta **6**:229, 1939-1940.

28. (*a*) Bubis and Swanbeck.[4e] (*b*) Achmatowicz, L.: Zentralbl. Chir. **63**:1585, 1936. (*c*) Jones, J. D. T.: Brit. J. Surg. **36**:49, 1948.

29. (*a*) Wasilijew: Kasansche med. Ztschr., 1909, p. 383; abstracted, Zentralbl. Chir. **37**:594, 1910. (*b*) Janutz, V.: Frankfurt. Ztschr. Path. **34**:446, 1926 (Case 1). (*c*) Fabris, U.: Gazz. internaz. med.-chir. **31**:476, 496, and 536, 1926; cited by Ferrandu.[5k] (*d*) Puccinelli, V.: Arch. ital. chir. **24**:70, 1929-1930. (*e*) Meyer-Wildisen, R.: Schweiz. med. Wchnschr. **1**:546, 1931. (*f*) Ciocca: Atti et mem. Soc. lomb. chir. **1**:525, 1933; cited by Ferrandu.[5k]

30. (*a*) Orlandi, E.: Gazz, med. di Torino, No. 40, p. 781, 1896; cited by Turnure[4b] and Naeslund.[2e] (*b*) Turnure.[4b] (*c*) Janutz,[29b] Case 2. (*d*) Fabris.[29c]

tomosis of the ileum.[31] Occasionally, a combination of the above entities is found in one patient. Gas cysts not associated with any other disease of the gastrointestinal tract are usually referred to as "primary" pneumatosis.

The distribution of the gas cysts within the abdominal cavity is shown in Table 3. It will be noted that the small bowel is most frequently involved in cases in which the cysts are associated with a lesion of the pyloric area, whereas the ileocecal location is most frequently encountered in the remaining group of cases. The latter includes 33 cases of "primary" pneumatosis. The possible significance of this finding will be discussed below. In many cases the cysts are found involving simultaneously various, widely scattered portions of the intestine. At the same time they may be found also in extraintestinal locations.

Among the less frequently encountered locations of cysts one finds the stomach,[32] the duodenum,[33] the gastrohepatic ligament,[34] the falciform ligament,[35] the parietal and diaphragmatic peritoneum,[36] the mesentery,[37] the mesocolon,[38] the omentum,[39]

TABLE 3.—*Distribution of Lesions*

Location of Gas Cysts	Diseases Associated with Gas Cysts: Diseases of the Pyloric Area	Other Associated Diseases	Total
1. Small bowel (except duodenum)	66	27	93
2. Small and large bowel	6	0	6
3. Small bowel and other sites *	25	7	32
4. Small and large bowel and other sites *	1	2	3
Total with small bowel involvement	98	36	
5. Large bowel	2	7	9
6. Cecum and surrounding area	5	29 †	34
7. Large bowel and other sites *	0	4	4
Total with large bowel involvement	7	40	
8. Various locations ‡	14	4	18
9. Unknown	5	9	14
Total	124	89 §	213

* These include mesentery, parietal peritoneum, diaphragmatic peritoneum, mesocolon, omentum, stomach, lymph nodes and falciform ligament.
† Fourteen are cases of "primary" pneumatosis.
‡ See text.
§ This total includes 33 cases of "primary" pneumatosis.

31. Mengis, O.: Radiol. Schriften **7**:222, 1938.

32. (*a*) Sloan.[4e] (*b*) Baetzner.[16e] (*c*) Hoffheinz, S.: Zentralbl. Chir. **62**:150, 1935. (*d*) Baumann-Schenker, R.: Acta radiol. **20**:365, 1939.

33. (*a*) Kolli, V. A.: Vrach. Zapiski Moskva **2**:215, 1895; abstracted, Ergebn. allg. Path. u. path. Anat. **5**:212, 1898. (*b*) Tuffier and Letulle, M.: Bull. Acad. méd. Paris **81**:5, 1919 (Case 2). (*c*) Garschin, W. G.: Westnik chirurgii i porgranichnich oblastei **3**:91, 1923; abstracted, Zentralbl. org. Chir. **25**:291, 1924. (*d*) Kemal, M.: Deutsche med. Wchnschr. **59**:1707, 1933 (Cases 1 and 2). (*e*) Tribedi, B. P.: Calcutta M. J. **38**:285, 1941.

34. Stori, T.: Clin. mod. **10**:481, 1904; cited by Turnure,[4b] Naeslund,[2e] and Ferrandu.[5k]

35. Pybus, F. C.: Brit. J. Surg. **21**:539, 1934.

36. (*a*) Viscontini, C.: Gazz. osp., No. 118, 1904, p. 1249, cited by Turnure,[4b] Naeslund,[2e] and Ferrandu.[5k] (*b*) Woltmann.[19a] (*c*) Dietrich: Das intestinale Emphysem, Thesis, Heidelberg, 1909; cited by Naeslund,[2e] and Ferrandu.[5k] (*d*) Romiti, C.: Ann. ital. chir. **3**:927, 1924. (*e*) Kopelowitz,[5g] Case 2. (*f*) Pybus.[35] (*g*) Sauser-Hall,[5m] Case 3. (*h*) Kaspar, M.: Zentralbl. Chir. **69**:226, 1942. (*i*) Ruckensteiner and Kux,[17f] Cases 1 and 3. (*j*) Coelho.[22b]

and lymph nodes.[40] It is of interest to note three cases with extremely widespread distribution of cysts,[41] involving various portions of the intestine as well as the mesentery, the peritoneum, the omentum, and the gastric ligaments. Two most unusual cases are that of Ruppanner,[42] in which cysts were found in a stump of nonfunctioning bowel, following ileocolostomy, and that of Fanchamps,[43] with cysts located within the pleura and the mediastinum in the presence of pulmonary tuberculosis which had been treated with bilateral pneumothorax. One rarely finds abdominal cysts not associated with bowel involvement, only eight cases being on hand.[44]

Pneumoperitoneum or even tension pneumoperitoneum is reported with increasing frequency in cases of the disease. Urban [45] reported, in 1910, a case in which spontaneous tension pneumoperitoneum occurred in a 13-year-old girl with pneumatosis cystoides intestinalis. The gas was accumulating so rapidly that a drain had to be inserted into the abdominal wall in order to assure comfort. Healing followed.

Several additional cases of pneumoperitoneum secondary to gas cysts have been reported,[46] owing to more frequent roentgenologic diagnosis of the disease.

The microscopic picture is characterized by the presence of cysts, predominantly in the serosa and subserosa of the bowel. Submucosal cysts are less common but when found are usually associated with serosal cysts. However, in "primary" pneu-

37. (*a*) Nigrisoli.[15] (*b*) Viscontini.[36a] (*c*) Bindi.[17b] (*d*) Mauclaire: Bull. mém. Soc. chir. Paris **45**:1334, 1919. (*e*) Schnyder, K.: Cor.-bl. schweiz. Aerzte **47**:289, 1917 (Case 2). (*f*) Kuder, H.: Zentralbl. Chir. **45**:69, 1918 (Case 2). (*g*) Tuffier and Letulle,[22b] Case 2. (*h*) Cristol and Porte.[23a] (*i*) Zuccola, P. F.: Riforma med. **37**:222, 1921. (*j*) Steindl.[24a] (*k*) Reverdin, A.: Rev. méd. Suisse Rom. **44**:542, 1924. (*l*) Baetzner.[16c] (*m*) Fabris.[29c] (*n*) Burhaneddin, A.: Zentralbl. Chir. **57**:647, 1930. (*o*) Englund, F., and Wahlgren, F.: Acta chir. scandinav. **76**:601, 1935. (*p*) Achmatowicz.[25b] (*q*) Onaca and Kovacs.[24b] (*r*) Tribedi.[32e] (*s*) Jones.[28c] (*t*) Dale and Pearse.[4n]

38. (*a*) Sherman, T., and Wilkie, D. P. D.: J. Path. & Bact. **14**:259, 1910. (*b*) Nitch and Shattock.[5c] (*c*) Barbosa, J. M.: Méd. ibera **15**:217, 1921. (*d*) Cascio, L.: Cultura méd. mod. Palermo, p. 403, 1922; cited by Ferrandu [5k] and Leo.[5l]

39. (*a*) Arzt.[5a] (*b*) Philip.[19b] (*c*) Tuffier and Letulle,[22b] Case 1. (*d*) Zuccola.[37l] (*e*) Chavanez, G.: Bull. et mém. Soc. chir. Paris **48**:636, 1922. (*f*) Garschin.[33c] (*g*) Reverdin,[37k] Case 1. (*h*) Tung and Ngai,[16a] Case 2. (*i*) Coelho,[23b] Case 2. (*j*) Sauser-Hall,[5m] Case 2. (*k*) Pozgay, I. von: Wien. med. Wchnschr. **91**:105, 1941. (*l*) Dale and Pearse,[4n] Case 2. (*m*) Capovilla, E.: Rass. med. sarda **53**:7, 1951; abstracted, J. A. M. A. **147**:352 (Sept. 22) 1951.

40. (*a*) Schnyder,[37e] Case 2. (*b*) Urban, H.: Fortschr. Geb. Röntgenstrahlen **55**:231, 1937. (*c*) Coelho,[23b] Case 2. (*d*) Volland, W.: Zentralbl. allg. Path. **46**:201, 1948-1949. (*e*) Paas, H.: Chirurg **20**:69, 1949.

41. (*a*) Zuccola.[37l] (*b*) Chavanez.[39e] (*c*) Dale and Pearse,[4n] Case 2.

42. Ruppanner, I.: Helvet. med. acta **10**:313, 1943.

43. Fanchamps, A.: Schweiz. Ztschr. Path. **8**:208, 1945.

44. (*a*) Stori.[24] (*b*) Bindi.[17b] (*c*) Cristol and Porte.[23a] (*d*) Coelho,[23b] Case 2. (*e*) Sauser-Hall,[5m] Case 3. (*f*) Capovilla,[39m] Case 2. (*g*) Urban.[40b] (*h*) Fanchamps.[43]

45. Urban, K.: Wien. med. Wchnschr. **60**:1750, 1910.

46. (*a*) Lamont.[11] (*b*) Chiray, M., and Lomon, A.: Presse méd. **44**:1771, 1936. (*c*) Mengis.[31] (*d*) Ribeiro.[22] (*e*) Dressler,[27] Cases 1 and 2. (*f*) Canessa, J. A. G.; Lorenzo y Losada, H.; Capurro, F. G., and Roglia, J. L.: An. Ateneo clin. quir. **7**:89, 1941. (*g*) Tribedi.[32e] (*h*) Druckmann and Schorr.[10b] (*i*) Frostberg.[22e] (*j*) Jones.[28c] (*k*) Burhaneddin.[37n] (*l*) Ruckensteiner and Kux,[17f] Case 2. (*m*) Gazin, Brooke, Lerner, and Price [4k]

matosis of the cecal area submucous location of cysts is the rule rather than the exception. The muscularis is the least frequently involved layer of the intestine. The mucosa of the affected segments of the bowel is usually reported as free of defects. This is particularly emphasized when the cysts are associated with a gastric or duodenal ulcer. Solution of the continuity of the mucosa in the form of tuberculous or nonspecific ulcerations, inflammatory lesions, or gaps due to the presence of parasites is occasionally reported in the remaining group of cases.

In practically all cases the cysts are at least partially lined by a layer of endothelial cells with eosinophilic protoplasm and small, dark, round nuclei. The lining cells have a tendency to coalesce to form large, multinucleated giant cells. The fact that in many surgically removed specimens the cysts were lined by simple cuboidal to columnar epithelium suggests that the giant cells are not necessarily an integral part of the lining. Nevertheless, the cyst lining, including giant cells, is very characteristic of the disease.

The giant cells appear in progressively larger numbers as the cysts undergo fibrosis. In due time the giant cells are sloughed off, and finally the cyst is bare of any lining. A clump of giant cells is then frequently seen lying in the center of a slit-like space surrounded by hyaline connective tissue. With progressing fibrosis and occlusion of the cyst the giant cells disappear.

In only two cases has foreign material been found within the giant cells. Turnure [4b] reported the presence of crystals, possibly of fatty acids. Jones [28c] reported the presence of doubly refractile bodies.

Within the connective tissue surrounding the cysts various inflammatory processes can take place. These reactions may range from a very active inflammation, characterized by eosinophilic leucocytes, plasmacytes and lymphocytes, to formation of granulomas with epithelioid cells. Within the granulomas one can find remnants of a few giant cells. Therefore it seems that the granulomas appear late in the course of the disease.

It is rare to find any inflammation of significance within the dense fibrous tissue surrounding the slit-like spaces filled with giant cells. In an attempt to reconstruct the sequence of events in the disease one could postulate the following steps as suggested by the present case.

1. Formation of cysts with simple endothelial lining.
2. Formation of giant cells.
3. Inflammatory reaction in the surrounding connective tissue.
4. Sloughing off of giant cells with concomitant fibrosis of surrounding stroma.
5. Diminution of the size of the cysts to the point of complete fibrosis with ultimate disappearance as scarring progresses.

Indeed, as it is reported below, there is excellent evidence that the cysts can disappear completely during life.

COURSE AND COMPLICATIONS OF PNEUMATOSIS CYSTOIDES INTESTINALIS

The early stages of the gas cysts are obscure. A case report by Mengis [31] is of interest. A 16-year-old girl underwent a laparotomy for release of adhesions which developed after perforation of an acutely inflamed appendix. A portion of ileum was also resected. The bowel at that time was free of gas cysts. When laparotomy

was performed a second time, four years later, pneumatosis of the small intestine was observed. Dale and Pearse [48b] reported a case in which a man 35 years of age was operated on for carcinoma of the stomach. At operation no cysts were seen. At autopsy, five weeks later, cysts were found in the submucosa of the jejunum and the ileum. Finally, Jones [28c] reported a case of a 63-year-old man who had undergone laparotomy for intestinal obstruction; no cysts were found. Two and one-half years later, on repeated laparotomy for tension pneumoperitoneum, typical pneumatosis was found, involving the colon and the mesentery. These three reports indicate that the disease can develop within a relatively short time. However, indications are still completely lacking as to the duration of the disease prior to clinical or pathological diagnosis.

There is considerable evidence that the cysts may disappear spontaneously. In 1900, Wikerhauser [47] reported a case of pneumatosis cystoides in a 35-year-old man. The cysts involving the ileum were seen on laparotomy, and the diagnosis was confirmed by histological examination. Two months later, the patient died of peritonitis and no trace of cysts was found. Several additional cases in which there was evidence of either complete or partial involution of the cysts have since appeared in the literature.[48a] Two cases of the disease with x-ray evidence of healing but without surgical or pathological confirmation have also been reported.[49] Cases of clinical improvement following simple exploratory laparotomy are numerous, although in some of these objective evidence of healing is lacking. The impression has thus been created, and occasionally stressed,[48b] that gas cysts of the intestine should be considered as a harmless, self-limited condition of no serious consequence.

However, Kadjan,[50] in 1902, reported the case of a 34-year-old woman who had undergone three laparotomies for pneumatosis cystoides within 4½ months. After the third intervention there was clinical evidence of improvement, but the cysts had not disappeared. This appears to be the first case in the literature implying that the disease may assume a chronic and prolonged course. A few similar reports with an adequate follow-up may be found. These are the cases observed by Gazin and associates,[48k] Reverdin [27k] (case *2*), with x-ray follow-up, and Parson and Parson.[49] The duration of the disease was 5 weeks, 6 months, and 2½ years, respectively.[51] It is conceivable that many more of the reported cases of the disease had a chronic course prior to autopsy.

Intestinal obstruction may complicate the course of pneumatosis cystoides. This was emphasized by Hahn [14] as early as 1899.

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47. Wikerhauser, T.: Liečnički Viestnik, No. 8, 1900; abstracted, Zentralbl. Chir. **27**:938, 1900.

48. (*a*) Nigrisoli.[15] (*b*) Mori, M.: Deutsche Ztschr. Chir. **38**:553 and 620, 1907-1908. (*c*) Lindström,[10b] Case *2*. (*d*) Tuffier and Letulle,[33b] Case 1. (*e*) Faltin, R.: Deutsche Ztschr. Chir. **131**:166, 1914. (*f*) Mills,[5b] Case *2*. (*g*) Silverstone, J.: Lancet **1**:129, 1928. (*h*) Berglund, S.: Acta radiol. **20**:401, 1939. (*i*) Jackson.[4b] (*j*) Povlsen, O.: Nord. med. **16**:3326, 1942.

49. (*a*) Lerner and Gazin.[41] (*b*) Chiray and Lomon.[48b]

50. Kadjan, A.: Russ. khir. Arch., St. Petersburg, No. 6, 1902; abstracted, Zentralbl. Chir. **30**:300, 1902.

51. Schorr and associates [40] recently reported a case of pneumatosis associated with a gastric ulcer in a 70-year-old man. The disease was followed roentgenologically for four years without therapy and subsequently confirmed on autopsy.

There appear to be four main ways in which the abdominal gas cysts may cause intestinal obstruction:

1. Submucous cysts may obliterate the lumen.
2. Volvulus may be induced by cysts.
3. An extrinsic mass of cysts may compress the intestine.
4. The bowel may be compressed by adhesions engendered by cysts.

Furthermore, a single case of intussusception due to gas cysts was reported by Ciocca.[29f]

1. Submucosal cysts, although not infrequently encountered, rarely cause elevation of the mucosa sufficient to interfere seriously with intestinal transit. However, two cases of partial intestinal obstruction due to submucosal cysts have been reported.[52] It is also pointed out in the literature [40b] that cysts of the submucosa will give rise to clinical manifestations earlier and in a more persistent manner than serosal cysts.

2. Volvulus complicating pneumatosis cystoides was found in the original case of Bang,[13] where a torsion of the sigmoid flexure of the colon was reported. Similar cases have been reported by Jones [28c] and Achmatowicz.[28b] Volvulus of the small bowel associated with pneumatosis has been reported by five authors.[53] The rotated segment of the intestine was covered with cysts in all cases except in that reported by Bang. Sauser-Hall [53m] considered the pneumatosis secondary to the volvulus, although his patient had an acute intestinal obstruction and died shortly after the onset of the disease. It would appear that the contrary is probably true and that the presence of gas cysts causing abnormal peristalsis brings about volvulus.

3. Large extrinsic masses of cysts have been described as a cause of intestinal obstruction. Six such cases are recorded in the literature.[54] Undoubtedly, masses of cysts can assume very large proportions. Lindström,[10b] as mentioned above, reported a case of a cluster of cysts of the size of a "child's head." However, it appears that most of such large structures are freely movable and do not interfere with intestinal transit. Obstruction, when it occurs, is usually associated with adhesions binding the mass of cysts to some surrounding organ.

4. Adhesions formed between the diseased loops of bowel or between the bowel and other organs have been reported by some observers.[55] The unusual feature of the adhesions is that cysts are present within them. Intestinal obstruction, due to such adhesions, was reported by Winands,[55a] Steindl,[24a] and Gazin and associates.[4k] Two additional cases reported by Vaz [5n] and Miranda, Monteiro, and de Carvalho [23d] most likely belong in the same category.

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52. (*a*) Lafourcade, M. J.: Bull. et mém. Soc. chir. Paris **45**:1309, 1919. (*b*) Bettoni.[21]

53. (*a*) Reverdin,[37k] Case 1. (*b*) Sauser-Hall,[53m] Case 2. (*c*) Jackson.[43b] (*d*) Paas.[40e] (*e*) Raffaelli.[16b]

54. (*a*) Wiesinger: Zentralbl. Chir. **37**:577, 1910. (*b*) Oidtman, A.: Netherlands Surgical Society, Dec. 17, 1911; abstracted, Zentralbl. Chir. **40**:349, 1913. (*c*) Bindi.[17b] (*d*) Tuffier and Letulle,[53b] Case 2. (*e*) Bubis and Swanbeck.[4e] (*f*) Parson and Parson.[4j]

55. (*a*) Winands, M.: Beitr. path. Anat. **17**:38, 1898. (*b*) Turnure.[43b] (*c*) Steindl.[24a] (*d*) Aljakritskij, V.: Vrach. delo **9**:1309, 1926; abstracted, Zentralbl. org. Chir. **36**:812, 1926. (*e*) Muzii, M.: Radiol. med. **20**:660, 1933. (*f*) Englund and Wahlgren.[37o] (*g*) Gazin, and others.[4k] (*h*) Dale and Pearse.[4n]

In the case which has been reported here, the intestinal obstruction was due to a combination of volvulus and compression of a segment of bowel, caused by adhesions. It appears that the volvulus was of very recent occurrence, since relatively little damage had been done to the wall of the involved loop of bowel. One assumes that the formation of adhesions preceded the volvulus and that both were due to gas cysts.

This case and the case of Gazin and associates [4k] coincide exactly in that the cysts formed a continuity between the adjacent loops of bowel. Probably—judging from published illustrations—this particular feature was present in several additional cases without being described. It is of interest to note that in loops of bowel thus affected, the serosal layers are completely replaced by cysts whereas the muscular layers appear well preserved. This suggests a sequence of events involving formation of adhesions as a result of pneumatosis, with the cysts subsequently extending into the adhesions. Indeed, in pneumatosis, as described above, the serosa of the bowel may undergo severe inflammatory changes, sufficient to explain formation of adhesions and destruction of the serosa.

CAUSE AND PATHOGENESIS OF GAS CYSTS

The opinion of the principal students of this entity is that the cysts are actually lymphatic vessels distended with gas. Stübel,[56] in a series of ingenious experiments, utilizing H_2O_2, has been able to fill the lymphatics of thin slices of various organs with oxygen. The picture of a section of intestine in which the lymphatics are distended with gas shows considerable resemblance to pneumatosis cystoides. On the other hand, some unsuccessful attempts have been made to reproduce the disease either by injecting gas into the lymphatic vessels of animals or by various other manipulations of the gastrointestinal tract.[57] Staudacher and Bencini,[58] by injecting colored fluid into the lymphatics of hogs, proved to their satisfaction that in these animals the disease is due to distention of lymphatics. In humans, various factors point toward the lymphatic origin of the cysts. Several authors report histological evidence that the cysts are connected with lymphatics.[59] The histological pattern of the disease and particularly the endothelial lining of the cysts are also suggestive of a vascular, most likely a lymphatic, origin. The occasional concomitant involvement of lymph nodes may also be interpreted in favor of involvement of the lymphatic system.

Most authors assume that the gas present within the lymphatics is the *primum movens* of the disease. The exact composition of the gas is as yet not definitely known. Naeslund [2e] has demonstrated conclusively that the gas does not have the

56. Stübel, A.: Arch. path. Anat. **244**:287, 1923.

57. (*a*) Nowicki.[10a] (*b*) Ciechanowski.[10d] (*c*) Miyake, H.: Arch. klin. Chir. **95**:429, 1911. (*d*) Estella, L., and de Castro, B.: Rev. cir. Barcelona **1**:141, 1931. (*e*) Tung and Ngai.[10a] (*f*) Menna, L.: Policlinico (sez. chir.) **47**:220, 1940.

58. Staudacher, V., and Bencini, A.: Chirurgia **4**:421, 1949; abstracted, Surg., Gynec. & Obst. **92**:421, 1949.

59. (*a*) Gröndahl, N. B.: Deutsche med. Wchnschr. **34**:913, 1908. (*b*) Demmer, F.: Arch. klin. Chir. **104**:402, 1914. (*c*) Schnyder.[37e] (*d*) Thalheimer, W.: Zentralbl. Chir. **40**:363, 1913.

same composition as air, and particularly that it has a very low oxygen content, contrary to frequent assumptions. He determined, after exposing the cysts to air for 20 minutes, that the oxygen content had increased from 0.5-1.4% to 13.1%.

The question whether the presence of gas is sufficient to account for the histological changes within the lymphatics remains unanswered by most authors. However, Wright,[60] by injecting gases into the subcutaneous tissue of animals under sterile conditions, was able to obtain a chronic inflammatory response with formation of epithelioid cells and even giant cells of Langhan's type around the artificially created emphysematous areas. He reported that after prolonged presence of gas there was formation of hyaline connective tissue between the cystic spaces. To the best of my knowledge, Wright's work appears to be the only experimental proof that a foreign gas present within tissue may cause chronic inflammation. The question whether a similar reaction can occur within the lymphatics is still open. It is conceivable that by causing an inflammatory reaction the gas produces a walling-off of a lymphatic channel with subsequent cyst formation.

There are two principal theories as to the origin of the gas: the bacterial theory and the mechanical theory.

The bacterial theory implies that the gas is formed by gas-producing microorganisms within the lymphatics or the tissues.

The most remarkable series of bacteriological studies was performed by Naeslund,[3e] who cultured from the cysts of hogs a gas-forming organism of the Escherichia coli group which he called Bacillus pneumatosis. Naeslund was able to obtain weakly positive serological reactions in diseased hogs, whereas healthy controls gave negative results. This author was unable, however, to reproduce cysts by injecting the bacteria into animals.

In the more recent literature, several authors have reported that organisms of the Esch. coli group were recovered from the cysts.[61] Several other authors [62] have reported failure to grow organisms, some also emphasizing the absence of anaerobic organisms, as well as the negative results in their search for fungi and parasites.

The strongest argument against the bacterial theory is, in my opinion, the fact that long-standing pneumoperitoneum occurs very frequently in the disease and that it is very rarely, if ever, associated with peritonitis. A similar view has been previously expressed by Dressler.[37]

The mechanical theory as applied to cases of gas cysts associated with gastric ulcer and pyloric stenosis implies that stomach gas, being under pressure because of obstruction, is forced into the lymphatics opened up by the ulcerative process and then distributed further by peristalsis. One would then have to assume that the gas travels along the lymphatics from the stomach to various distant and frequently widely spaced portions of the gastrointestinal tract, and produces cysts there, without producing any along its course. In only one case [16a] has any communication been demonstrated between stomach and cysts.

60. Wright, A. W.: Am. J. Path. **6**:87, 1930.

61. (*a*) Nimet, B.: Zentralbl. Chir. **61**:1986, 1934. (*b*) Baumgartner, O.: Helvet. med. acta **10**:771, 1943. (*c*) Sauser-Hall,[5m] Case 2. (*d*) Pybus.[35]

62. (*a*) Sawada, B.: J. Orient. Med. **9**:66, 1928. (*b*) Lamont.[11] (*c*) Urban.[40b] (*d*) Paas.[40e] (*e*) Gazin, and others.[4k]

A variant of the mechanical theory has been very recently postulated by Stiennon,[63] who suggested that under pressure the gas spreads from the obstructed stomach or other portions of the gastrointestinal tract along the mesentery. Such a mechanism would indeed account for the predominantly serosal location of cysts and would also explain how widely separated portions of the bowel could be simultaneously involved.

Stiennon admitted that there is actually little evidence to substantiate his theory. Furthermore, gas under pressure dissecting along the mesenteric planes would most likely cause severe vascular disturbance due to compression of vessels. This is not seen in cases of pneumatosis cystoides. Here, once again, the absence of cyst formation along the assumed path of the gas is relevant.

Even though the mechanical theory appears unsatisfactory as applied to cases of gas cysts associated with pyloric stenosis and with an otherwise intact mucosa of the bowel, it should certainly be seriously thought of in considering the cases of pneumatosis associated with ulcerative intestinal lesions. There the intestinal gas could penetrate into the local lymphatics, causing cyst formation. Indeed, in the latter group of cases, submucosal cysts are frequently encountered. As has been pointed out before, involvement of the ileocecal area is found with high frequency in the group of cases not associated with a gastric or a duodenal ulcer. Appendiceal lesions in the form of acute inflammation with or without an ulcer are occasionally reported in such instances. It is of interest to note that in 14 of 33 cases of so-called primary pneumatosis, with no other lesions of the gastrointestinal tract, the cysts were located in the cecum and the ascending colon. The possibility exists that in these cases investigation of the appendix would yield an ulcerative lesion accounting for the gas penetration into the lymphatics.

A few additional cases illustrate vividly the possibility of mechanical factors operating in the formation of gas cysts. Drew [25] described gas cysts that had developed in a portion of small intestine proximal to a point of obstruction due to an impacted gallstone. Onaca and Kovacs [24b] described gas cysts in a portion of large bowel proximal to a point of obstruction created by an adhesive band. Xanthopulides [26] (Case 1) observed gas cysts in a segment of small intestine found within the thoracic cavity in a case of diaphragmatic hernia. Puccinelli [29d] beautifully demonstrated channels, formed by parasites, opening from the mucosa to the cysts. Thus the mechanical theory finds justification in a certain percentage of cases.

The inadequacies of the bacterial and mechanical theories have caused several observers to postulate that gas is produced locally within the lymphatics. Falcone [64] thought that respiratory dysfunction of cells causes accumulation of gas. Cascio [35d] believed that there are respiratory epithelial elements within the villi which can produce gas. Mair [65] advocated that the cyst lining is capable of producing gas. Joest [66] and, independently, Masson [67] assumed that gas is produced in the lymphatics as a result of a chemical reaction. In a very elaborate discussion, Masson pointed out that in hogs fed dairy waste products pneumatosis is frequent. He

63. Stiennon, O. A.: A. M. A. Am. J. Dis. Child. **81**:651 (May) 1951.

64. Falcone, R.: Policlinico (sez. chir.) **31**:636, 1924.

65. Mair, W.: M. Chron. **14**:422, 1907.

66. Joest, E.: Arch. path. Anat. **234**:524, 1921.

67. Masson, P.: Rev. méd. Suisse Rom. **45**:470, 1925; Ann. anat. path. **2**:541, 1925.

assumed that excessive intestinal acidity due to faulty carbohydrate metabolism causes liberation of carbon dioxide within the lymphatics.

Biester, Eveleth, and Yamashiro [68] succeeded in producing gas cysts in hogs by feeding them polished rice. The gas cysts were formed in intestinal wall, mesentery, lymph nodes and muscle. Since there was no evidence of impaired metabolism of carbohydrates or proteins, these authors assumed that the permeability of the intestinal mucosa or gas was increased, owing to unknown factors. In a somewhat later communication [69] it was shown that whole corn, unpolished rice, and skimmed milk powder partially protected the animals from cyst formation. It was thus established that in hogs the disease could be reproduced by diet deficient in a yet unknown factor.

It is certainly very tempting to consider the human disease as a result of a deficiency. The high frequency with which diseases causing serious disturbances of the digestive process precede and coexist with gas cysts would be an indication in favor of the deficiency theory. The unknown deficiency could conceivably be associated with alteration of the hydrogen ion concentration of the intestinal content with the result that gas is produced in the lymphatics according to the idea expressed by Joest and by Masson.

It is by no means unusual to find marked variations in the degree of deficiency disease involvement among members of a population exposed to similar dietary and living conditions. This is true for scurvy, pellagra, and rickets and could apply also to pneumatosis cystoides of the intestine and account for its sporadic occurrence.

For the sake of completeness it should be added that a neoplastic theory was formulated by Bang [13] but has not had widespread acceptance. The gross and histological patterns of the lesion, as well as its course, do not appear to favor the neoplastic theory. Scattered additional reports contained original ideas as to the etiological factors of the disease. Fabris,[29c] Janutz,[29b] and Puccinelli [29d] attributed the cysts to the action of intestinal parasites. Von Hacker and von Hibler [70] considered the circulating blood as the source of the gas.

In summary it appears that at least two and possibly more explanations of the origin of the cysts could be invoked:

(*a*) The mechanical theory, applied to cases with demonstrable mucosal defects, or channels of communication, extending between a portion of the gastrointestinal tract and the cysts. It is suggested that in many cases of so-called primary pneumatosis, particularly with cecal involvement, a careful investigation of the appendix would probably yield a portal of entry for the gas.

(*b*) The chemical deficiency theory, serving best at the present time to explain the origin of the lesions in cases with intact intestinal mucosa. This group includes most of the cases associated with lesions of the upper gastrointestinal tract, such as gastric or duodenal ulcer or even esophageal stenosis due to ingestion of lye.

In either event, predisposing factors have to be considered in order to explain the extreme rarity of the disease. Striking differences in the distribution of the gas cysts according to the associated disease (Table 3) indicate the possibility that distinct sets of etiological factors may be in operation.

68. Biester, H. E.; Eveleth, R. F., and Yamashiro, Y.: J. Am. Vet. M. A. **41**:714, 1936.

69. Eveleth, D. F., and Biester, H. E.: Am. J. Hyg. **27**:364, 1938.

70. von Hacker and von Hibler: Wien. klin. Wchnschr. **16**:368 and 430, 1903.

DIFFERENTIAL DIAGNOSIS OF LESIONS SIMILAR TO PNEUMATOSIS

I have previously pointed out that at least two and possibly more pathogenic processes may result in the formation of the characteristic disease picture of pneumatosis cystoides. It appears very doubtful that true cyst formation ever occurs unless gas penetrates into the lymphatics.

Diffuse emphysema associated with an infection due to gas-forming microorganisms characteristically shows diffuse distribution of gas in tissue spaces and may therefore be differentiated from the abdominal gas cysts. Such emphysema, although encountered in the stomach [71] and the gall bladder,[72] is rarely encountered in the intestines.[73]

Acute enteritis due to the more common pathogens may be associated with abundant gas production within the lumen of the intestine and, at the same time, cause mucosal erosions. In addition, it has been emphasized that in infants acute enteritis of either catarrhal or purulent type is associated with definite edema of the wall and dilatation of subepithelial lymphatics.[74] Recently, an increasing number of cases have been reported in which "intestinal emphysema" occurred in infants suffering from acute intestinal disorders.[75] In all these cases the disease was characterized by the presence of gas-filled spaces and was assumed to be closely related to pneumatosis.

Whether the above type of emphysema, lacking, as it does, any type of cyst lining, is a manifestation of pneumatosis is open to serious question. Furthermore, the association of classic pneumatosis and acute enteritis is exceedingly rare.[20] It appears to me that true gas cysts due to gas that has penetrated into lymphatics are rare in infants and small children. Those cases in which there is evidence of cyst lining [76] are accepted, and the others are considered as cases of emphysema, possibly a terminal event, with intestinal gas penetrating into the intestinal wall generally and not selectively into the lymphatics. The same criticism appears to be valid for certain cases of gas cysts in adults, which have therefore been excluded from these statistics.[77]

Gas cysts of the intestine should be differentiated from enterogenous cysts. The enterogenous cyst is usually single, although occasionally multiloculated. It is usually

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71. (*a*) Fraenkel, E.: Arch. path. Anat. **118**:526, 1889. (*b*) Sundberg, O.: Nord. med. **51**:303, 1918. (*c*) Morton, J. J., and Stabins, S. J.: Ann. Surg. **87**:848, 1928. (*d*) Weens, H. S.: Am. J. Roentgenol. **55**:588, 1946.

72. (*a*) Hegner, C. F.: Arch. Surg. **22**:993, 1932. (*b*) Stevenson, C. A.: Am. J. Roentgenol. **51**:53, 1944.

73. (*a*) Jeppson, K.: Zentralbl. allg. Path. **27**:409, 1916. (*b*) Siegmund, H., in Handbuch der speziellen pathologischen Anatomie und Histologie, edited by F. Henke and O. Lubarsch, Berlin, Springer-Verlag, 1929, Vol. 4, Pt. 3, p. 403.

74. Siegmund,[73b] pp. 352-363.

75. (*a*) Maas, H.: Berl. klin. Wchnschr. **41**:401, 1904. (*b*) Moore.[48] (*c*) Botsford, T. W., and Krakower, C.: J. Pediat. **13**:185, 1938. (*d*) Lindsay, J. W.; Rice, E. C., and Selinger, M. A.: Arch. Path. **30**:1085 (Nov.) 1940. (*e*) Judge, D. J.; Cassidy, J. E., and Rice, E. C.: Arch. Path. **48**:206 (Sept.) 1949 (17 cases). (*f*) Stiennon,[62] 2 cases.

76. (*a*) Moore,[48] all 4 cases. (*b*) Botsford and Krakower,[75c] Case 2.

77. (*a*) Dupraz, A.: Arch. méd. expér. et anat. path. **9**:282, 1897. (*b*) Vallas and Pinatelle: Lyon méd. **97**:215, 1901. (*c*) Thorburn, W.: M. Chron. **4**:255, 1902.

intramural, located in the distal ileum, and is lined by normal intestinal mucosa. It usually occurs in children and young adults. Only about 60 cases of this rare entity have been published.[78]

Lymphangioma of the peritoneum, although a very rare tumor, can, according to descriptions of it,[79] resemble cystic pneumatosis. The presence of lymph rather than gas, as well as the lack of giant cells within the lining, should make the differentiation possible.

Histological pictures similar to those encountered in pneumatosis cystoides are occasionally noted in fat necrosis and sclerosing lipogranulomatosis.[80] Large cystic spaces lined with large macrophages and giant cells are seen. A fat stain revealing the fat content of such cysts and their location within fat tissue should prove sufficient for diagnosis.

Attention should be called to the fact that histologically the lymph nodes involved in Whipple's disease [81] are similar to the lymph nodes involved in pneumatosis cystoides.[82] Giant cells might be present in either disease, but associated intestinal change should help in differentiating intestinal lipodystrophy from pneumatosis cystoides.[83]

It appears of importance to mention that emphysematous vaginitis [84] and emphysematous cystitis,[85] with a histological picture similar, if not identical with, that of intestinal gas cysts, have been repeatedly described in the literature. All three of these disease pictures are considered by some authors as being closely related. Not having had any experience with emphysematous vaginitis or cystitis, I am unable to evaluate and compare them with pneumatosis cystoides intestinalis.

CLINICAL AND X-RAY DIAGNOSIS

The gas cysts may interfere with intestinal transit. This manifests itself clinically by vomiting, abdominal distention, vague abdominal complaints, and occasionally diarrhea. Cecal pneumatosis has been frequently mistaken for appendicitis.

Occasionally an abdominal mass was palpable which on laparotomy was found to consist of cysts.[86] Usually, however, the presenting symptom is that of the associated disease, for example, pyloric stenosis due to a gastric ulcer.

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78. (*a*) Hughes-Jones, W. E. A.: Brit. J. Surg. **22**:134, 1934-1935. (*b*) Pachman, D. J.: Am. J. Dis. Child. **58**:485 (Sept.) 1939. (*c*) Pinninger, J. L.: Arch. Dis. Child. **22**:59, 1947.

79. Reichel, P., and Staemmler, M.: Neue deutsche Chir. **33B**:67, 1933.

80. Smetana, H. F., and Bernhard, W.: Arch. Path. **50**:296 (Sept.) 1950.

81. (*a*) Apperly, F. L., and Copley, E. L.: Gastroenterology **1**:461, 1943. (*b*) Odesski, L., and Burdison, W. R.: Arch. Path. **49**:307 (March) 1950.

82. (*a*) Schnyder.[37e] (*b*) Urban.[40b]

83. In a very recent communication Creese [4p] has also emphasized certain similarities between lipodystrophy and gas cysts. The subject certainly deserves further investigation.

84. Kilian,[51] review of literature.

85. (*a*) Mills, R. G.: J. A. M. A. **94**:321 (Feb. 1) 1930; Surg., Gynec. & Obst. **51**:545, 1930. (*b*) Ravich, A., and Katzen, P.: J. A. M. A. **98**:1256 (April 9) 1932. (*c*) Burns, R. A.: J. Urol. **49**:808, 1943.

86. (*a*) Hahn.[14] (*b*) Wiesinger.[54a] (*c*) Bubis and Swanbeck.[4e] (*d*) Trias Pujol, A.: Rev. méd. Barcelona **1**:233, 1924 (Case 2). (*e*) Zeno: Rev. méd. Rosario **14**:297, 1924. (*f*) Sawada.[62a] (*g*) Tung and Ngai,[56a] Case 2. (*h*) Ciocca.[29f] (*i*) Baumgartner.[61b] (*j*) Lerner and Gazin.[41] (*k*) Friedman, I.: J. Clin. Path. **2**:91, 1949. (*l*) Gerundo and Chang.[18f]

As a matter of fact, the correct diagnosis has been made clinically but very rarely. Recently, emphasis has been laid upon the x-ray appearance of the lesions. Barjon and Dupasquier [87] and Moreau [88] were the first to give accurate descriptions of x-ray findings in cases of gas cysts. French, Scandinavian, German, and recently American roentgenologists [89] have pointed out the deformity of the intestinal contour and the reticulated, cyst-like appearance of the lesion. It is also emphasized that the so-called Chilaiditi sign,[90] or interposition of a loop of bowel between the liver and the diaphragm, is often found in cases with small-bowel involvement. The frequent occurrence of spontaneous pneumoperitoneum [46] is of value in clinical and x-ray diagnosis. The pneumoperitoneum may persist for a long period. It is occasionally a tension pneumoperitoneum and may cause the presenting clinical symptom. As recently emphasized by Pruvot and Leger,[91] gas cysts should always be considered in the differential diagnosis of spontaneous pneumoperitoneum.

THERAPY

The rarity of the disease accounts for the complete lack of a uniform approach to the problem of therapy. It would appear that in early cases of cysts, not complicated by adhesions, the therapy of the basic disease, i. e., gastric ulcer, is indicated, without any attempt at bowel resection. In "primary" pneumatosis resection of the affected segment of bowel should probably follow a period of clinical observation, since there is definite evidence that the cysts may disappear spontaneously.

Presence of adhesions probably warrants a more radical surgical approach in view of the definite possibility of bowel obstruction.

SUMMARY AND CONCLUSIONS

Abdominal gas cysts represent a well-defined morphological entity with characteristic gross and microscopic findings.

In 58% of the cases the development of the cysts is associated with a lesion of the pyloric area, principally a peptic ulcer, frequently of a stenotic type. In this group of cases there is preponderant involvement of the small bowel.

In 15.4% of the cases there is so-called primary pneumatosis, unassociated with any other lesions. In this group of cases there frequently is isolated involvement of the cecal area with submucosal location of the cysts.

That intestinal gas shall have penetrated into lymphatics appears to be a condition *sine qua non* of formation of gas cysts.

87. Barjon, F., and Dupasquier, D.: Lyon méd. **121**:565, 1913.

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It is probable that at least two and possibly more mechanisms can account for formation of cysts.

It is suggested that in cases of "primary" pneumatosis with cecal involvement a careful examination of the appendix would disclose a portal of entry for the gas.

From the differential diagnostic viewpoint, only endothelium-lined, gas-containing cysts should be accepted as representing pneumatosis cystoides intestinalis. Presence of giant cells is helpful but irrelevant for diagnosis.

Certain similarities between the lymph node involvement in cases of gas cysts and that in cases of intestinal lipodystrophy (Whipple's disease) are noted.

Complications of the disease include chronic, prolonged course and intestinal obstruction.

Wider knowledge of the characteristic x-ray picture and of the frequent occurrence of spontaneous pneumoperitoneum should help in establishing the correct diagnosis of the entity clinically.

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RELATIONSHIP OF NEMATODE LARVAE TO GENERALIZED SARCOIDOSIS

Report of a Case and Review of the Literature

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MANY various etiologic agents have been suggested as causes of generalized sarcoidosis. The chief etiologic questions have been concerned with whether or not sarcoidosis represents some form of tuberculosis.[1] Other agents mentioned in discussion of the causation of this disease are Brucella,[2] Mycobacterium leprae,[3] Treponema pallidum,[4] protozoa,[5] viruses,[6] fungi,[7] beryllium,[8] and foreign bodies, especially silicon-containing material.[9] The possibility that the disease represents a neoplastic process also has been considered.[10]

Recently, a case was studied which may throw some light on the cause of an undetermined percentage of cases of generalized sarcoidosis.

REPORT OF CASE

A 14-year-old white girl was first admitted to The Children's Hospital in 1944 for a rash, pruritus, and pain in the genitalia and anus of six weeks' duration. Five to six weeks previous to admission, a "red sore" had developed in the rectum. A local physician had considered this to be a hemorrhoid. After treatment with sitz baths, it improved for a short time but recurred to involve the vagina and vulva. Occasionally, blood was noted in the stools, and there was rectal tenesmus. A slightly raised, indurated rash was noted in the genital region, involving

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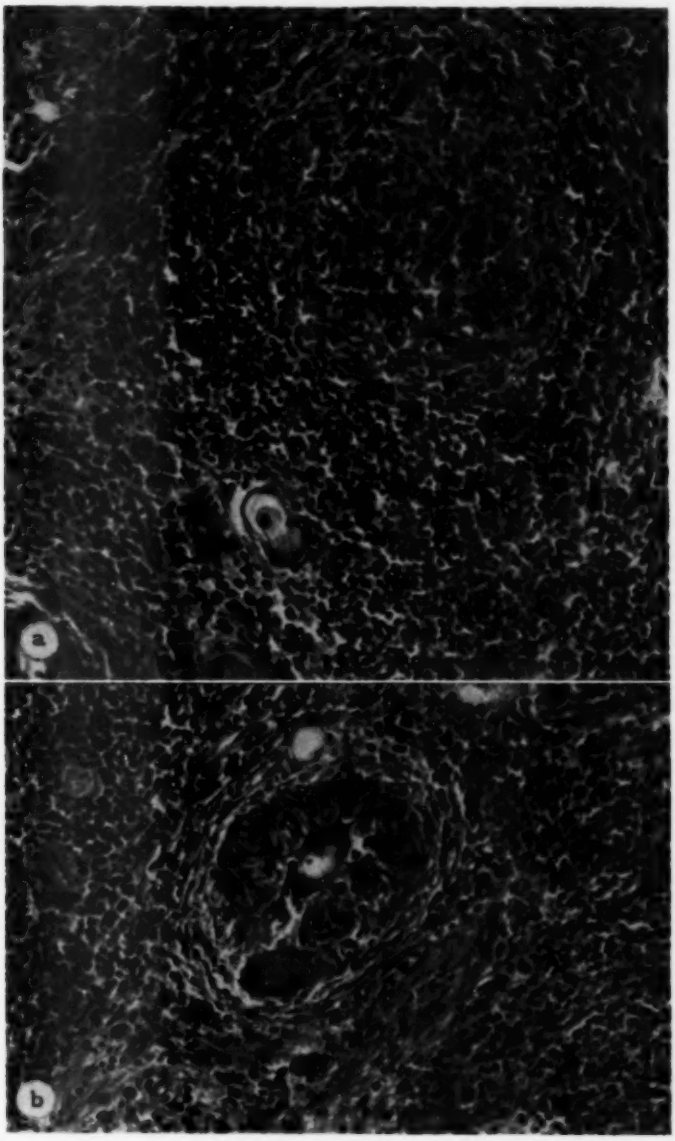

Fig. 1.—Subcutaneous tissue of the perineum: (*a*) One large granuloma and a portion of another are visible. Diffuse plasmacytic infiltration and scattered lymphocytes and eosinophiles can be seen between the granulomas. A concentrically lamellated body with a central eosinophilic structure is lying free in the subcutaneous tissue. This was interpreted as representing a larva of an intestinal nematode. (*b*) A body similar to that portrayed in *a*, surrounded by palisading histiocytes and a Langhans giant cell. (Eosin-methylene blue; × 210.)

the medial aspect of both buttocks, the anus, perineum, vulva, labia majora, and the introitus. There were bilateral soft, tender, enlarged inguinal nodes, but no generalized lymphadenopathy was present.

The patient was readmitted in 1946 because she had passed five to six watery, mucoid stools daily and bright red blood at frequent intervals by anus. Biopsy of the skin was performed, and a diagnosis of "lymphogranuloma venereum or sarcoidosis" was made. Roentgenologic examination of the chest revealed considerable prominence of each hilus, particularly of the left. The Frei test, on two occasions, and a complement-fixation test for lymphogranuloma venereum gave negative results. The concentration of hemoglobin was 11.2 to 11.5 gm. per 100 cc. of blood. The number of erythrocytes per cubic millimeter of blood varied from 4,450,000 to 4,960,000; the number of leucocytes varied from 4,600 to 7,000, and the differential count was normal. The total serum protein was 6.14 gm. per 100 cc. with 3.96 gm. of albumin and 2.18 gm. of globulin. The result of a tuberculin test using 0.1 mg. of old tuberculin was negative.

The patient was admitted for the last time in 1947 because of red, indurated papules, about the size of a quarter, slowly forming on the lower portions of both legs. They were tender and considered most likely to be lesions of sarcoidosis. She had lost 10 lb. (4.5 kg.) in weight and had an afternoon temperature of 102 to 103 F. Her erythrocyte sedimentation rate was 87 mm. per hour. A second biopsy specimen of the skin was interpreted to suggest sarcoidosis.

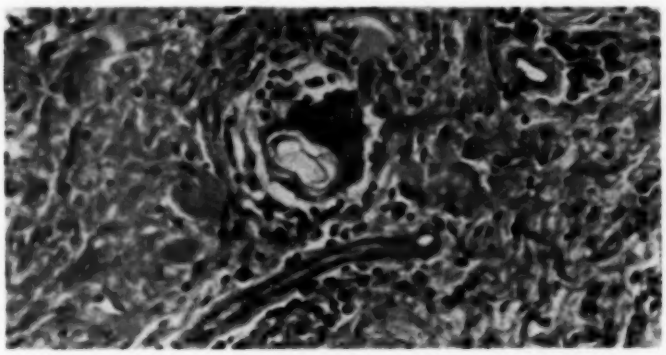

Fig. 2.—Subcutaneous tissue of the perineum: A later stage than that shown in Figure 1*b*, showing a phagocytosed "larva" forming a Schaumann body. The central eosinophilic mass has disappeared at this stage of development. (Eosin-methylene blue; × 210.)

Roentgenologic examination of the colon revealed the major portion extensively diseased, with gross alteration of contour and mucosal pattern. The appearance was consistent with that of advanced ulcerative colitis. The radiologist could not be certain whether the condition could be classified as a true manifestation of sarcoidosis or whether the lesion was that of some other disease. The patient was discharged and followed in the outpatient department, where her condition remained about the same when she was last seen on Jan. 19, 1950.

Histologic examination of the first surgical specimen yielded many interesting observations. The tissue was fixed in Zenker's solution and 10% formalin (formaldehyde solution U. S. P. diluted 1:10). The sections were stained with hematoxylin and eosin, the Hotchkiss-McManus stain, Mallory's aniline blue, Weigert's elastic tissue stain, Wilder's reticulum stain, phosphotungstic acid-hematoxylin, and Ziehl-Neelsen stain. The corium and subcutaneous tissue contained focal aggregates of histiocytes, frequently with one to three giant cells. The granulomas were surrounded by numerous plasmacytes, lymphocytes, and eosinophiles. The subcutaneous tissue and corium between the granulomas were diffusely infiltrated with plasmacytes and a lesser number of lymphocytes and eosinophiles. A fine reticulum network was noted in and about the epithelioid cells forming the granulomas. Fibrinoid necrosis was noted occasionally in the centers of the granulomas. Tubercle bacilli were not demonstrated.

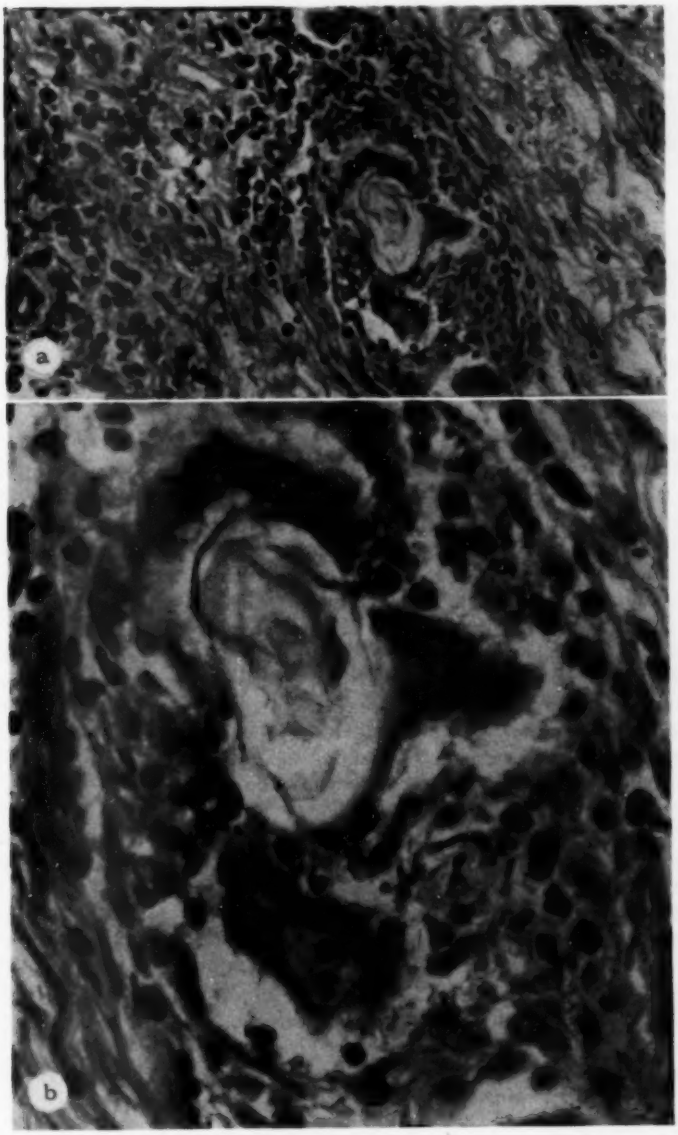

Fig. 3.—Subcutaneous tissue of the perineum: (*a*) Schaumann body similar to that in Figure 2. The concentric lamellae are more apparent, and the entire body seems to have swelled and increased in size. (Eosin-methylene blue; × 210.) (*b*) Higher magnification of *a*, revealing details of the Schaumann body. (Eosin-methylene blue; × 760.)

A most interesting feature was the observation of doubly refractile laminated bodies, each with a central eosinophilic tubular structure, which were scattered throughout the lesions. Compressed nuclei were noted at the peripheries of these bodies. By studying various sections, it was possible to reconstruct the formation of Schaumann bodies from these lamellated structures. In the earliest stage (Fig. 1*A*), the body lay free in the subcutaneous tissue, surrounded by a diffuse infiltration of plasmacytes, lymphocytes, and eosinophiles. At a distance, granulomas were discerned. The next stage (Fig. 1*B*) revealed a body surrounded by palisading histiocytes, forming epithelioid cells and a giant cell. The body was still lying free and showed no evidence of phagocytosis at this time. During the next stage (Figs. 2 and 3) the body was phagocytosed by giant cells and was found in the cytoplasm of these cells, producing a Schaumann body. At this time, the central tubular mass had disappeared, the lamellation was more pronounced, the bodies were larger and swollen, and, rarely, a portion protruded from a giant cell.

In the early stages the bodies stained with the Hotchkiss-McManus stain, but this characteristic was lost in the later stages. No elastic tissue or collagen was identified in the bodies. They looked remarkably like nematode larvae. They were shown to Dr. Donald Augustine, professor of tropical public health, Harvard Medical School, who thought that the appearance was consistent with that of the larvae of Strongyloides stercoralis.

COMMENT

Since this first case was studied, three additional cases of sarcoidosis have been seen in which it was possible to consider a nematode as cause. The first of these has been presented in detail in another paper [11] and will only be summarized here. The case was that of a 64-year-old man who was not suspected clinically of having sarcoidosis. However, at postmortem examination, granulomas were present in lungs, the spleen, the liver, lymph nodes, and the thyroid capsule. There was no caseation necrosis, and no tubercle bacilli were demonstrated. Schaumann bodies which closely resembled chitinous material were encountered in the lungs.

In the next case, biopsy of the liver of a patient who had generalized sarcoidosis revealed granulomas in all sections; generally, they were limited to the portal triads. Chitinous material was associated with many of the granulomas.

The last case was that of a 27-year-old Negro who had clinical and roentgenologic manifestations of sarcoidosis. Surgical biopsy of the gastrocnemius muscle revealed numerous granulomas and an occasional doubly refractile body which was considered to be a parasitic larva.

As far as could be determined from the literature, nematodes never have been incriminated before in the etiology of sarcoidosis. The most common nematode in climates where sarcoidosis appears to be prevalent is Ascaris lumbricoides. This nematode is widespread in distribution. S. stercoralis has a cosmopolitan distribution, but it is much more common in warmer climates, where it parallels the incidence of hookworms. It has been reported in North Temperate climates—for example, in Canada and Russia.

The life cycles of these parasites can be found depicted in textbooks of parasitology;[12] only a brief summary will be given here.

Embryonated ova of A. lumbricoides are ingested and hatch in the small intestine, where the larvae penetrate the intestinal wall and enter the portal circulation.

11. Jaques, W. E.: Sarcoidosis: A Review and a Proposed Etiologic Concept, Arch. Path., this issue, p. 558.

12. Belding, D. L.: Textbook of Clinical Parasitology Including Laboratory Identification and Technic, New York, Appleton-Century-Crofts Company, Inc., 1942. Faust, E. C.: Human Helminthology: A Manual for Physicians, Sanitarians and Medical Zoölogists, Ed. 2, Philadelphia, Lea & Febiger, 1939.

They pass through the liver to the lungs, where they are filtered out into the alveoli, pass up the bronchi, trachea, and larynx, and are swallowed to mature into adult worms in the intestine.

S. stercoralis can develop different types of life cycles. Generally, the rhabditiform larvae are found in the stool. They may develop directly into filariform larvae, or they may first form free-living males and females. The latter lay ova, which in turn form rhabditiform larvae and finally filariform larvae. The filariform larvae penetrate the skin and enter the venous circulation, filter out in the lungs, pass up the bronchi and trachea, and are swallowed, to develop into adult worms in the intestines. Occasionally, the rhabditiform larvae are present in the intestine for a long enough time to develop into filariform larvae. These larvae then pass through the intestinal wall and follow a course similar to that of the larvae of A. lumbricoides. The latter life cycle is called the hyperinfective or superinfective type.

The organs most commonly involved by nematode infestation are, of course, the intestines and organs, that are in the path of larval migration, the liver, the lungs, the air passages, and the skin. In experimental ascariasis, larvae may enter the general circulation if too many are injected.[13] Suyemori [14] fed embryonated ova of A. lumbricoides to guinea pigs and a monkey, and retinal hemorrhages and anisocoria ensued. The larvae had been carried to the uveal tract and were particularly prevalent in the choroid. An infiltration of round cells, many eosinophiles, polymorphonuclear leukocytes, and foreign-body giant cells were noted in the choroid. A few larvae were present in the ocular organs of the guinea pigs, but the majority had been returned to the heart. No larvae were found in the monkey, although pathologic changes in the organs could be verified. Calhoun [15] described an 8-year-old boy who had acute iridocyclitis associated with second degree glaucoma. An object which resembled a larva of an intestinal parasite projected into the pupil. It was viewed by a parasitologist, who expressed the opinion that it was the larval form of A. lumbricoides. The parasite died, but an attempt to remove it failed. Boettiger and Werne [16] described a case in which two adult worms of A. lumbricoides were found in the right ventricle of the heart at postmortem examination. The mesenteric lymph nodes frequently are involved in A. lumbricoides infestation. Kyle, McKay, and Sparling [17] found S. stercoralis in the gastrointestinal tract, the mesentery and mesenteric lymph nodes, the lungs and trachea, the heart, the liver, and the gall bladder. Experimentlly, larvae of A. lumbricoides have been reported in the kidneys.[18]

The degree to which tissues respond to nematode infestation varies with the degree of resistance and reactivity of the host. Blackie [18] administered thousands of embryonated ova of Ascaris megalocephala to nonimmune rabbits, guinea pigs, and mice and studied histologic preparations of the livers, lungs, and kidneys. There was an eosinophilic response in the periportal areas, occasionally associated with granulomas and mononuclear cells. Generally, larvae were not associated with the granulomas. In the lung a "vermifuge pneumonia" was noted, with intra-

13. Witenberg, G.: Acta med. orient. **4**:363, 1945.
14. Suyemori, S.: Taiwan Igakkai Zasski **1**:239, 1925.
15. Calhoun, F. P.: Arch. Ophth. **18**:963, 1937.
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18. Blackie, W. K.: J. Helminthol. **8**:93, 1930.

alveolar hemorrhage, histiocytosis of the alveoli, and aggregates of hemosiderin-laden phagocytes. The kidneys displayed necrosis of tubular epithelium in the distal nephrons. Kerr [19] produced a true acquired immunity in guinea pigs through repeated infection with pig ascarides. He studied the histologic changes in the cecum, the liver, and the lungs in immune and nonimmune guinea pigs. He found an eosinophile and polymorphonuclear leukocyte response to predominate in the nonimmune animal, and only a slight granulomatous reaction was encountered occasionally. The resistant guinea pigs displayed a predominantly granulomatous inflammatory response, and verminous nodules with a foreign-body reaction were noted frequently. Furthermore, it was noted that the granulomas were not always associated with larvae. In a fatal case of ascariasis described by Einhorn, Miller, and Whittier [20] considerable fibrosis and inflammatory exudate were noted throughout most of the intra-alveolar stroma. Histiocytes and other mononuclear cells were the predominating types of cells, and eosinophiles and larvae were not seen. Granulomatous lesions also were noted in sections of the intestines by Kyle, McKay, and Sparling.[17] Fragments of larvae were noted in the centers of these granulomas. These authors also referred to literature concerning tumor formations consisting of granulation tissue containing parasites.

Sensitivity to A. lumbricoides has been demonstrated by numerous observers.[21] Generally, some time must elapse after exposure before sensitivity is evident. Antigens composed of a protein [22] and a polysaccharide fraction [23] have been made, and passive transfer of antibodies has been demonstrated.[24]

Girges [25] found a peak incidence of A. lumbricoides infestation in persons between 10 and 20 years of age. He stated that the infestation rarely occurred during the first year of life because of breast feeding. The disease affects all classes of people but is most prevalent in rural areas.

Recently, a syndrome characterized by chronic eosinophilia and visceral changes has been described.[26] In this syndrome there are transient infiltration of the lung, resembling miliary tuberculosis radiologically, hepatomegaly, splenomegaly, and hyperglobulinemia. Perlingiero and György,[26a] in a biopsy of the liver, observed an exudative eosinophilic infiltration and granulomas. The total serum protein was as high as 10.64 gm. per 100 cc., with the globulin accounting for 7.53 gm. per 100 cc. No ova or parasites were found in the stools, but an adult ascaris was vomited during the hospital stay. These authors assumed that, in all probability, the findings were secondary to ascariasis. More recently, Mercer and his co-workers [26b] studied a case in which four larvae were found at biopsy of the liver.

19. Kerr, K. B.: Am. J. Hyg. **27**:28, 1938.

20. Einhorn, N. H.; Miller, J. F., and Whittier, L.: Am. J. Dis. Child. **69**:237, 1945.

21. (*a*) Jones, T. L., and Kingscote, A. A.: Am. J. Hyg. **22**:406, 1935. (*b*) Brunner, M.; Altman, I., and Bowman, K.: J. Allergy **15**:2, 1944. (*c*) Davidson, A. G.; Baron, B., and Walzer, M.: J. Allergy **18**:359, 1947. (*d*) Rocha e Silva, M., and Graña, R.: Arch. Surg. **52**:523, 1946. (*e*) Oliver-Gonzáles, J.: J. Infect. Dis. **72**:202, 1943. (*f*) Kerr.[19] (*g*) Einhorn and Miller.[20]

22. Jones and Kingscote.[21a] Brunner and others.[21b] Davidson and others.[21c]

23. Campbell, D. H.: J. Infect. Dis. **59**:266, 1936.

24. Kerr.[19] Einhorn and others.[20] Jones and Kingscote.[21a] Brunner and others.[21b]

25. Girges, R.: J. Trop. Med. **37**:162, 1934.

26. (*a*) Perlingiero, J. G., and György, P.: Am. J. Dis. Child. **73**:34, 1947. (*b*) Mercer, R. D.; Lund, H. Z.; Bloomfield, R. A., and Caldwell, F. E.: Ibid. **80**:46, 1950.

Otherwise the histologic picture was similar to that of the case described previously. The value for total serum protein reached 8.55 gm. per 100 cc., with 5.41 gm. accounted for by globulin. On most occasions the results of tests for ova or parasites in the stools were negative, and on only one examination was an adult male form of A. lumbricoides passed. Conversely, Zuelzer and Apt [27] described eight cases, with similar clinical, radiologic, and laboratory findings, in which no parasites could be found and in five of which there was a negative cutaneous reaction to a test for Ascaris.

The syndrome just described bears a great similarity to Loeffler's syndrome and tropical eosinophilia. In 1942, von Meyenburg [28] described four cases in which there were transitory lung infiltrations and eosinophilia. At postmortem examination, the predominating exudative cells were eosinophiles, but macrophages and giant cells were encountered. In one patient, forms of A. lumbricoides were found in the intestine, and the liver was similar to those previously described. Sommer [29] stated that in Loeffler's syndrome the infiltration of the lung is an allergic reaction of the lung of a sensitized subject to only a few larvae of A. lumbricoides. Bayley and his associates [30] studied the lungs of a 59-year-old woman with Loeffler's syndrome and found granulomatous lesions with central "fibrinoid" necrosis, epithelioid cells, peripheral lymphocytes, plasmacytes, and eosinophiles. The arterioles showed necrotizing arteritis and arteriolitis in a few instances. No larvae or tubercle bacilli were demonstrated, and the results of a tuberculin test using 1.0 mg. of old tuberculin had been negative. The photomicrographs in his paper closely resembled those taken in cases of sarcoidosis.

The geographic distribution of generalized sarcoidosis seems to be widespread, but Michael and his associates,[31] studying the incidence of the disease among inductees in the Army of the United States during World War II, demonstrated a greater incidence in the southeastern portion of the country. These authors stressed the apparent rural distribution of their cases.

SUMMARY AND CONCLUSIONS

A case of sarcoidosis has been presented which probably represents a response to nematode larvae. In connection with this case, the formation of a Schaumann body has been depicted, probably for the first time. Three additional cases in which chitinous material was considered to be present have been described briefly. The portion of the literature pertaining to helminths that has a bearing on sarcoidosis has been reviewed. The geographic distribution of cases of sarcoidosis and nematode infestation, the organs involved, the histologic appearance of involved tissues, and the laboratory observations are considered to favor a cause-effect relationship in some cases.

27. Zuelzer, W., W., and Apt, L.: Am. J. Dis. Child. **78**:153, 1949.
28. von Meyenburg, H.: Arch. path. Anat. **309**:258, 1942.
29. Sommer, E.: Schweiz. med. Wchnschr. **73**:1132, 1943.
30. Bayley, E. C.; Lindberg, D. O. N., and Baggenstoss, A. H.: Arch. Path. **40**:376, 1945.
31. Michael, M. Jr.; Cole, R. M.; Beeson, P. B., and Olson, B. J.: Am. Rev. Tuberc. **62**:403, 1950.

SARCOIDOSIS

A Review and a Proposed Etiologic Concept

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THE PURPOSE of this review is to clarify the meaning and the terminology of sarcoidosis and to present various etiologic considerations of the disease. The major portion of the paper will be devoted to the etiology and the pathology of this condition. Two cases which may facilitate the discussion will be described.

TERMINOLOGY

A distinction must be made between generalized sarcoidosis and focal sarcoid lesions. The literature is confusing in regard to the various forms of the disease. In this paper the term "sarcoidosis" will be limited to the generalized form of the disease, which involves particularly lymph nodes, lungs, spleen, skin, uveal tract, liver, and bone marrow. It is characterized histologically by the presence of granulomatous lesions without caseation necrosis or tubercle bacilli. The term "sarcoid lesions" will be used to describe local granulomatous lesions, which are particularly common in the hilus of the lung. These lesions are considered to represent a tissue reaction to one of a variety of agents.

HISTORICAL DATA

Sarcoidosis was first described by Jonathan Hutchinson [1] in 1875 and was called "Mortimer's malady" because his patient was named Mortimer. Fourteen years later, Besnier [2] gave a more detailed clinical description of the skin manifestations. In 1899, Boeck [3] recorded the pathologic histology of these granulomatous lesions as observed in the skin and described an associated lymphadenopathy. Heerfordt [4] first described fever, bilateral uveitis and parotitis, and palsy of certain of the cranial nerves, especially the seventh. Because of the similar pathologic pictures and the occasional coexistence of Boeck's disease and Heerfordt's syndrome, Bruins Slot [5] suggested that uveoparotid fever was merely another form of sarcoidosis. Schaumann [6] described a generalized disease affecting primarily

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1. Hutchinson, J.: Arch. Surg., London **9**:307, 1898.
2. Besnier, E.: Ann. dermat. et syph. **10**:333, 1889.
3. Boeck, C.: J. Cutan. & Genito-Urin. Dis. **17**:543, 1899.
4. Heerfordt, C. F.: Arch. Ophth. **70**:254, 1909.
5. Bruins Slot, W. J.: Nederl. tijdschr. geneesk. **80**:2859, 1936.
6. Schaumann, J.: Sur le lupus pernio: Mémoire présenté en novembre 1914 à la Société française de dermatologie et de syphiligraphie pour le prix Zambaco.

the "lymphohematopoietic apparatus" and only incidentally the skin. Jüngling [7] first described lesions of bones. The disease has masqueraded under a number of names in the past, such as "Mortimer's malady," "Besnier-Boeck-Schaumann disease," "Heerfordt's disease," "uveoparotid fever," "lupus pernio," "Jüngling's disease," "osteitis tuberculosa multiplex cystica," "lymphogranuloma benignum," and "sarcoid," or "sarcoidosis." In May, 1934, the Réunion dermatologique de Strasbourg [8] devoted itself entirely to suggesting a name for this condition. They suggested that the name be changed from "*la maladie de Boeck*" to "*la maladie Besnier-Boeck*." In the United States of America it generally has been referred to as "sarcoid," "sarcoidosis," or "Boeck's sarcoid." In this paper the term "sarcoidosis" will be used. The term "sarcoid" is derived from two Greek roots meaning "flesh" and "form." Boeck proposed this term because he believed the histologic picture resembled the small cells of sarcoma.

INCIDENCE

It is difficult to assess the true incidence of clinically significant sarcoidosis. Rubin and Pinner [9] and Pinner [10] reviewed the literature up to 1944 and found 54 cases seen at postmortem examinations. Fisher,[11] in 1948, described 94 cases from the Johns Hopkins Hospital alone. In nine of these the diagnosis was made or verified at postmortem examination; in all but a few of the others biopsies were made on lymph nodes, skin, lid nodules, muscles, or other tissues. On the other hand, Ustvedt [12] noted only 58 cases reported in the literature up to 1948. Freiman,[13] in a masterly review of the literature, suggested that there were well over 1,000 cases of this disease and related syndromes. Schönholzer [14] reported an incidence of 0.13 per thousand in the Swiss Army. Dr. John B. Barnwell [15] has on record at the Army Institute of Pathology, Washington, D. C., nearly 400 specimens obtained for biopsy from soldiers who had sarcoidosis. Scott,[16] in more than 300 histologic examinations of lymph nodes excised to establish the diagnosis of Hodgkin's disease, found sarcoidosis in 1 of every 11 cases. Cone [17] reported 12 cases of sarcoid in 5,164 children, an incidence of 0.23%. The incidence appears to vary with the awareness of the disease among internists and pathologists. Probably it is much more common than is generally believed. Undoubtedly, in many instances it presents no symptoms and is an incidental finding at postmortem examination.

Age.—People of all ages are affected with this condition, but predominantly it appears to be a disease of early adult life. Freiman [13] stated that the incidence of the disease reaches a peak in persons between the ages of 15 and 50 years, with

7. Jüngling, O.: Fortschr. Geb. Röntgenstrahlen **27**:375, 1920.
8. Hannesson, H.: Brit. J. Tuberc. **35**:88, 1941.
9. Rubin, E. H., and Pinner, M.: Am. Rev. Tuberc. **49**:146, 1944.
10. Pinner, M.: Am. Rev. Tuberc. **37**:690, 1938.
11. Fisher, A. M.: Tr. Am. Clin. & Climatol. A. **59**:58, 1947.
12. Ustvedt, H. J.: Tubercle **29**:107, 1948.
13. Freiman, D. G.: New England J. Med. **239**:664, 1948.
14. Schönholzer, G.: Schweiz. med. Wchnschr. **77**:585, 1947.
15. Barnwell, J. B.: Tr. Am. Clin. & Climatol. A. **59**:73, 1947
16. Scott, R. B.: Brit. M. J. **2**:777, 1938.
17. Cone, R. B.: J. Pediat. **32**:629, 1948.

some cases reported involving infancy. Leitner [18] stated that the maximum incidence occurs in persons between the ages of 20 and 40 years. In 29 of the 52 patients described by Riley [19] the disease occurred in the third decade. Roos [20] observed the disease in a girl 4 years old and cited two other probable cases involving children, the youngest being 4 months of age. Cone [17] reported the disease occurring in 12 children ranging from 9 to 15 years of age, with an average age of 11.8 years. In a series of 19 proved cases Hauser [21] noted the average age of the patients to be 29.9 years, with the youngest patient 9 years and the oldest 63 years of age. Forty-two cases in which the patients' ages varied from 11 to 68 years, with an average age of 27.5 years, were reported by Oppenheim and Pollack.[22] Reisner [23] recorded 35 cases in which the patients' ages ranged from 8 to 40 years. Five cases reported in Scandinavian literature by Bruce and Wassén [24] revealed a similar age relationship. It would seem that the disease occurs in persons of all ages, but the greatest number of cases occur in the third and fourth decades.

Sex.—There appears to be an appreciable sex difference. Most authors (e. g., Cone [17] and Riley [19]) have reported a higher incidence in females than in males. Reisner,[23] in reporting a series of 35 cases, described 24 female and 11 male patients. On the other hand, Pinner,[10] reporting 25 cases seen at postmortem examinations, stated that the disease occurred in males in 13 instances and in females in 7; in 5 instances the sex was not reported. Nickerson [25] described six cases seen at postmortem examinations, three in males and three in females.

Race.—Most reports from the United States show an increased incidence of this disease among the colored races. Freiman [13] cited an incidence of 86% of the cases reported in New York City as affecting Negroes, 80% of those in Philadelphia, and 42% of those in San Francisco. In 83% of the series of cases reported from Baltimore by Fisher [11] the patients were Negroes. Katz and his associates [26] and Billow [27] stated that the disease occurs most often among Negroes, Puerto Ricans, and Indians. The report of Oppenheim and Pollack [22] reflected an opposite trend, with 30 white and 12 Negro patients. Stone [28] expressed the belief that the white race is more commonly affected. Certainly, the largest number of cases have been reported in the literature of the Scandinavian countries, and in that region the vast number of persons with the disease are white-skinned individuals. On Feb. 11, 1948, in a conference on sarcoidosis held under the auspices of the National Research Council, Division of Medical Sciences, Army Institute of Pathology, it was reported that, from material gathered during World War II, the

18. Leitner, S. I.: Der Morbus Besnier-Boeck-Schaumann; chronische epitheloidzellige Reticuloendotheliose sive Granulomatose, Basel, Benno Schwabe & Co., 1942, pp. 102-104.
19. Riley, E. A.: Am. Rev. Tuberc. **62**:231, 1950.
20. Roos, B.: Arch. Dis. Childhood **59**:280, 1937.
21. Hauser, H.: J. Oklahoma M. A. **39**:395, 1946.
22. Oppenheim, A., and Pollack, R. S.: Am. J. Roentgenol. **57**:28, 1947.
23. Reisner, D.: Am. Rev. Tuberc. **49**:289, 1944.
24. Bruce, T., and Wassén, E.: Acta med. scandinav. **104**:63, 1940.
25. Nickerson, D. A.: Arch. Path. **24**:19, 1937.
26. Katz, S.; Cake, C. P., and Reed, H. R.: New England J. Med. **229**:498, 1943.
27. Billow, B. W.: J. Mt. Sinai Hosp. **9**:164, 1942.
28. Stone, C. T., Jr.: New Orleans M. & S. J. **98**:369, 1946.

estimated incidence of sarcoidosis in Negroes was 16 times as great as that in white soldiers. In summary, it would appear that all races are involved but that in the United States there seems to be a greater incidence among dark-skinned individuals.

Geographic Distribution.—Sarcoidosis is world-wide in distribution. Michelson [29] stated that the geographic location appeared to have some importance. The Scandinavians have led in the number of articles published. Freiman [13] recorded a world-wide distribution, including cases from Japan. Barber [30] reported a case involving a man from Honduras, Clearkin and his associates [31] described a case occurring in the Caribbean region, and Hurley and Hughes [32] described two patients from Australia. The disease was not reported in Spain until 1942, when Noguer-More [33] reported a case.

All levels of society are afflicted with this disease, although it appears to be more common among persons from the lower economic group. Cone [17] stated that

TABLE 1.*—*Two Hundred Twenty-Six Cases of Sarcoidosis in Army Inductees: Regional Distribution by Birthplace Compared with Army Inductees by Region*

Region †	Number of Inductees in Thousands: November, 1940, to October, 1946	Number of Cases of Sarcoidosis by Birthplace	Cases of Sarcoidosis per 100,000 Inductees
White			
North	4,676	19	.41
South	1,919	43	2.24
West	790	3	.38
Total	7,385	65	.88
Negro			
North	254	4	1.58
South	633	156	24.63
West	16	1	6.11
Total	903	161	17.81
Grand total	8,288	226	2.73

* From Michael, Cole, Beeson, and Olson,[34] with slight modification in form.
† Regions as designated by the National Office of Vital Statistics:
North = New England, Middle Atlantic, East North Central, and West North Central states.
South = South Atlantic, East South Central, and West South Central states.
West = Mountain and Pacific states.

the disease is more common among rural folk living in the North Temperate Zone. An epidemiologic study of 350 histologically proved cases among inductees in the United States Army in World War II was made by Michael and his associates.[34] They found a heavy concentration in the southeastern portion of the country when the cases were compiled according to the birthplaces of the patients. The birthplaces were predominantly rural (Table 1). In metropolitan Atlanta, Ga. (population, approximately 500,000), no cases were found, while in Lakeland, Ga. (population, approximately 1,000), there were two cases of sarcoidosis.

29. Michelson, H. E.: J. A. M. A. **136**:1034, 1948.
30. Barber, H. W.: Proc. Roy. Soc. Med. **39**:92, 1945.
31. Clearkin, P. A.: Bettencourt-Gomes, S. C., and Bornstein, A.: Caribbean M. J. **7**:13, 1945.
32. Hurley, L. E., and Hughes, J. F.: M. J. Australia. **2**:238, 1942.
33. Noguer-More, S.: Actas dermo-sif. **33**:905, 1942.
34. Michael, M., Jr.; Cole, R. M.; Beeson, P. B., and Olson, B. J.: Am. Rev. Tuberc. **62**:403, 1950.

ORGANS INVOLVED

Practically every organ and tissue of the body has been involved by this disease, according to clinical and pathologic reports. A glance at Table 2 will show that the lungs, lymph nodes, spleen, skin, liver, bone and marrow, and uveal tract are involved most frequently.

Skin.—Initially, the disease was believed to involve the skin only, but, largely because of the work of Schaumann,[6] it was found to involve primarily the "lymphohematopoietic system." According to Ormsby and Montgomery,[35] the skin lesions manifest themselves as nodules, papules, or plaques that are few to numerous and occur on the face, on the back of the shoulders, and on the extensor surfaces of the arms. Subcutaneous nodules (Darier-Roussy) frequently develop slowly, usually without subjective symptoms. "As a rule, they are limited to various areas on the trunk and are imperfectly symmetrical." Lupus pernio (Besnier) consists of "erythematous areas and plaques which are infiltrated, thickened, bluish red, and usually symmetrically disposed. It occurs on the nose, face, ears, forehead, fingers, and dorsal surfaces of hands and occasionally on the toes." These authors noted that occasionally sarcoidosis is associated with lupus erythematosus.

One can readily appreciate the multitude of skin lesions clinically classified as sarcoidosis. Harrell [36] pointed out that distortion and destruction of the nares and involvement of the scalp and of the mucous membranes or skin around the rectum and perineum are seen. Usually, the palms and the soles are spared. Schaumann [37] stated that no case is known in which the skin alone was attacked. Rakov and Tayler [38] reported three cases in which there was no skin involvement. McCort and his co-workers [39] described 27 patients who had sarcoidosis, only two of whom had cutaneous lesions. Irgang [40] stated that sarcoid tumors of the skin have a higher incidence in Negroes. According to Michelson,[29] we shall continue to find the first evidence in the skin because internal lesions, even though they precede cutaneous lesions, provoke no symptoms.

Lymph Nodes.—In most series of cases, the lymph nodes appear to be involved more frequently than any other part of the body. Katz and his associates [26] stated that the most common initial observation is enlargement of lymph nodes. Bernstein [41] stated that involvement of the lymph nodes is the most frequent manifestation of the disease. All groups of lymph nodes are involved. In Reisner's [23] series of 35 cases the cervical nodes were involved in 28, the axillary in 25, the inguinal in 25, the epitrochlear in 19, the auricular in 12, the submaxillary in 8, the femoral in 4, and the submental in 2. It will be noted that only the superficial glands were represented, as his series consisted of patients examined clinically only. Generally, the hilar and mediastinal nodes are reported to be the most frequently involved internal chain. McCort and his co-workers [39] described 28 cases in which the

35. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, Ed. 7, Philadelphia, Lea & Febiger, 1948.

36. Harrell, G. T.: J. Bowman Gray School Med. **1**:1, 1943.

37. Schaumann, J.: Brit. J. Dermat. **48**:399, 1936.

38. Rakov, H. L., and Tayler, J. S.: J. Lab. & Clin. Med. **27**:1284, 1942.

39. McCort, J. J.; Wood, R. H.; Hamilton, J. B., and Ehrlich, D. E.: Arch. Int. Med. **80**:293, 1947.

40. Irgang, S.: Arch. Dermat. & Syph. **56**:659, 1947.

41. Bernstein, S. S.: J. Mt. Sinai Hosp. **12**:1045, 1946.

TABLE 2.—*Percentage of Organ and Tissue Involvement in Previously Reported Series*

Author	Cases Reported	Proof	Lymph Nodes	Lungs	Skin	Eye	Bone and Marrow	Spleen	Heart	Liver	Kidney	Central Nervous System	Gastro-intestinal Tract	Tonsils	Parotid Glands	Endocrine Glands
Ricker and Clark [23] *	195	Biopsy	....†	35.9	21.0	8.7	17.4	8.2	8.7	1.0	2.6	1.5	...	...	...	0.5
Fisher [11]	94	Autopsy (9) Biopsy (85)	75	83	36	41	11	20	11	16	5	13	...	...	8.5	...
Riley [19]	52	Biopsy	100	87	25	29	13	40	...	37	...	...	...	...	4	...
Reisner [28]	35	Biopsy	100	94.2	....	...	20	22.8	5.7	17.1	...	5.7	...	...	11.4	...
Friedman [29]	29	Autopsy	72.4	100	41.7	...	48.2	72.4	...	58.6	24.1	...	17.2	10.4	...	...
Rubin and Pinner [5]	26	Autopsy	73	69.2	30.7	3.8	15.1	53.8	7.6	38.4	15.1	15.1	11.5	7.6	3.8	...
Ricker and Clark [23] *	22	Autopsy	77.2	81.8	....	4.5	4.5	77.2	13.6	81.8	22.7	13.6	4.5	...	...	9.0
Nickerson [25]	6	Autopsy	50	66.6	0	...	66.6	83.3	16.6	...	0	0	...	...	...	...

* Ricker and Clark's series is divided into cases in which biopsy was performed and cases seen at postmortem examination to show the difference between clinical and pathologic involvement.

† This sign (...) denotes that involvement was "not recorded"; 0 denotes that "no involvement was found."

diagnosis was made after biopsy; roentgenologic evidence of intrathoracic lymphadenopathy was present in each instance. Fisher [11] pointed out that the nodes may be generally involved or only isolated groups may be enlarged. Hall [42] stated that splenomegaly and mesenteric lymphadenopathy are noted and that the disease may be confused with Hodgkin's disease and tuberculosis. Many times there may be no actual enlargement, yet biopsy of a node may disclose histologic evidence of sarcoidosis.

Lungs.—All observers agree that the lungs are frequently involved in sarcoidosis. Bernstein [41] remarked that pulmonary lesions appear at some time during the evolution of the disease in about 90% of the reported cases. Hall,[42] in a review article, concluded that clinically the disease is encountered most frequently in the thorax, next in the peripheral nodes, and then in the skin, the eye, and the bones. In all of Hauser's patients who had sarcoidosis there was roentgenologic evidence of chest disease.[21] McCort and his associates [39] observed enlargement of the intrathoracic nodes in 27 of their 28 patients. Of the 42 patients described by Oppenheim and Pollack,[22] 20 had roentgenologic evidence of the disease in the chest and peripheral manifestations, 14 had roentgenologic evidence of disease in the chest only, and 8 had peripheral manifestations only. According to Bernstein and Sussman,[43] five groups of intrathoracic changes were noted from a radiologic standpoint: (1) bilateral, frequently symmetrical enlargement of hilar and bronchial lymph nodes without evidence of pulmonary infiltration, (2) enlargement of mediastinal lymph nodes with variable degrees of infiltration of the pulmonary parenchyma, (3) miliary lesions simulating those of miliary tuberculosis, (4) discrete nodular infiltration with or without enlargement of hilar nodes, and (5) diffuse and confluent infiltration, which may represent a transition from other forms of sarcoidosis. King [44] made an important contribution by noting that in 60% of 37 patients studied by serial roentgenograms the disease cleared completely or almost completely in from seven weeks to three years, with an average of 22 months. The incidence of thoracic involvement varies with the stage of the disease in which changes are sought. Bruce and Wassén [24] explained the paucity of pulmonary symptoms by the fact that the lesions occur along the lymph channels and in the interstitial tissues, and therefore, to a large extent, the lungs remain air-conductive. Nickerson [25] pointed out that the pulmonary lesions are pleural or subpleural, peribronchial, or septal. Tice and Sweany [45] noted pulmonary vascular endarteritis producing vascular obstruction, which probably led to changes diagnosed as Ayerza's disease. As mentioned previously, the majority of pulmonary lesions regress, but Mallory [46] noted that sarcoidosis produced pulmonary fibrosis in six cases. Vascular and lymphatic lesions were noted in the lungs, especially in the interalveolar and intralobular septums, by Schaumann.[27] Riley [19] found cor pulmonale in 8% of 52 cases, with granulation tissue encroaching on the pulmonary vascular bed.

Eye.—The eye is afflicted in a significant number of cases of sarcoidosis. The cornea and the uveal tract may be the only affected portions, or these structures

42. Hall, I. M.: Post Grad. M. J. **23**:233, 1947.
43. Bernstein, S. S., and Sussman, M. L.: Radiology **44**:37, 1945.
44. King, D. S.: Am. J. Roentgenol. **45**:505, 1941.
45. Tice, F., and Sweany, H. C.: Ann. Int. Med. **15**:597, 1941.
46. Mallory, T. B.: Radiology **51**:468, 1948.

may be involved along with the parotid gland or the lacrimal gland, or with both. Sniderman [47] stated that 10% of the patients with sarcoidosis display iritis of the nodular type. Likewise, Cameron and Dawson [48] and Dawson [49] reported that the eyes are infiltrated in 10% of the cases. Savin,[50] in 1934, reported on 66 published cases of uveoparotid fever and found 9 in which there was enlargement of the lacrimal glands. No biopsies were made, however. Stuart,[51] in 1944, found about 100 cases of sarcoidosis or Heerfordt's disease recorded in the literature up to 1940, only 20 of which had been reported from North America. Kaplan,[52] reviewing 100 reported cases, found that ocular improvement was presented in 43. The uveal tract was involved in 28 cases, the lids in 7, the lacrimal glands in 9, and the conjunctiva in 6. In uveoparotitis the facial nerve frequently is paralyzed. Lewis [53] described a patient with uveoparotitis, proved by biopsy, which was associated with Adie's syndrome. It should be noted that Symmers [54] has expressed the belief that all cases of Mickulicz' disease are of lymphomatous origin.

Bone and Marrow.—The incidence of bone and marrow involvement in sarcoidosis is much more difficult to assess. Clinical and radiologic studies, especially those of the bones of the hands, are much more common than biopsies and postmortem studies. Generally, the extremities are not examined post mortem, and sections of phalanges rarely are taken. Katz and his associates [26] stated that 10 to 20% of the cases of sarcoidosis involve phalanges, metacarpals, and metatarsals. Tarsals, carpals, and long bones may be affected. Stone [28] noted that bone lesions occur in 20% of the cases. Ellis [55] and Eichenlaub and Sandler [56] pointed out that the lesions are solid and not cystic as they appear on roentgenologic examination. Schaumann [37] noted that the marrow is the starting point of the alterations in bones. A search of the available literature provided only one bona fide case of phalangeal lesions proved by biopsy or postmortem examination. Stoll [57] described a 14-year-old boy with a swelling of the middle finger seen on roentgenologic examination, but no biopsy was performed. Hollister and Harrell [58] described a patient in whom there was replacement of the marrow cavity of a phalanx, but tubercle bacilli were recovered from inoculated guinea pigs. Rubin and Pinner [9] described marrow involvement in 4 of their 26 cases seen at postmortem examination. In three of these there was definite tuberculosis; a microscopic section was not prepared in the fourth case. Newns and Hardwick [59] described a 2-year-old boy with fusiform swelling of the phalanges of both hands seen at roentgenologic examination. Biopsy revealed material similar to tuberculous granulation tissue, but there was no caseation, there were no tubercle bacilli,

47. Sniderman, H. R.: Am. J. Ophth. **24**:675, 1941.
48. Cameron, C., and Dawson, E. K.: Edinburgh M. J. **49**:736, 1942.
49. Dawson, E. K.: Edinburgh M. J. **49**:743, 1942.
50. Savin, L. H.: Tr. Ophth. Soc. U. Kingdom **54**:549, 1934.
51. Stuart, B. M.: Am. J. M. Sc. **208**:717, 1944.
52. Kaplan, M.: Am. J. Ophth. **31**:83, 1948.
53. Lewis, G. E.: Brit. M. J. **1**:552, 1941.
54. Symmers, D.: Arch. Path. **45**:73, 1948.
55. Ellis, F. A.: Acta med. scandinav. **104**:221, 1940.
56. Eichenlaub, F. J., and Sandler, I. L.: Am. J. Roentgenol. **39**:596, 1938.
57. Stoll, H. F.: Ann. Int. Med. **10**:1588, 1937.
58. Hollister, W. F., and Harrell, G. T.: Arch. Path. **31**:178, 1941.
59. Newns, G. H., and Hardwick, C.: Arch. Dis. Childhood **14**:78, 1939.

and tubercle bacilli could not be recovered from inoculated guinea pigs after 11 weeks. Nickerson [25] observed that the vertebral marrow was involved in three of his six cases seen at postmortem examination, and the femoral marrow in one. Hall [42] thought that study of marrow obtained by sternal punctures might establish a definite diagnosis during life. Michelson [29] made an unequivocal diagnosis of sarcoidosis during life in one case. Hauser [21] described a patient who had destructive lesions in the first six cervical vertebrae and in the anterior ends of the fourth and fifth ribs. Biopsy of a spinous process was reported by Dr. Henry L. Jaffe to show sarcoidosis. It should be borne in mind that when bone is involved, there is a nidus in the marrow with granulomatous inflammation, destruction of portions of the medulla, and thinning of the cortices. In summary, it would seem that histologic proof of the nature of these osseous lesions of the hands is much less common than the literature leads one to believe.

Spleen.—The reported incidence of splenic involvement in cases of sarcoidosis varies widely, depending on whether the diagnosis was based on clinical or on postmortem examination. Nickerson [25] found microscopic evidence of splenic involvement at postmortem examination in five of his six cases. Friedman [60] reported that in 21 of 29 cases of sarcoidosis microscopic evidence of disease of the spleen was shown post-mortem. He stated that from a histologic standpoint the spleen is the second most common site of involvement in generalized sarcoidosis. He noted also that the "pure form" of splenic sarcoidosis, with no lesions outside the spleen, probably is nonexistent. McCort and his associates [39] observed the disease in 28 patients from a clinical and a roentgenologic standpoint and found splenomegaly in only 3. This shows the marked disparity between the pathologic and the clinical reports. Crane and Zetlin [61] reported a case of hemolytic anemia which was considered to be secondary to Boeck's sarcoid. Chevallier and Fiehrer [62] described a patient who had splenomegaly and in whom lesions of skin and lymph nodes, characteristic of sarcoidosis, later developed. The spleen was removed, with amelioration of symptoms and disappearance of skin lesions, but, later, hepatomegaly developed, irregular fever occurred, and the patient died. Glanzmann [63] discussed at length the necessity of differentiating the splenomegaly and hepatomegaly of sarcoidosis of children from such diseases as Banti's syndrome and hemolytic anemia. Partenheimer and Meredith [64] reported a case of splenomegaly with hypersplenism attributed to sarcoidosis, with amelioration of symptoms by splenectomy. James and Wilson [65] described a case of sarcoidosis with spontaneous rupture of the spleen.

Heart.—Salvesen [66] was the first to describe an electrocardiogram indicating a bundle branch block and normal rhythm in a case of sarcoidosis. The cardiac abnormality was attributed to a myocardial nodule, but there was no postmortem examination to confirm the diagnosis. Longcope and Fisher [67] reported 31 cases of

60. Friedman, M.: Am. J. Path. **20**:621, 1944.
61. Crane, A. R., and Zetlin, A. M.: Ann. Int. Med. **23**:882, 1945.
62. Chevallier, P., and Fiehrer, A.: Sang **15**:555, 1942-1943.
63. Glanzmann, E.: Ann. pædiat. **165**:125, 1945.
64. Partenheimer, R. C., and Meredith, H. C., Jr.: New England J. Med. **243**:810, 1950.
65. James, L., and Wilson, A. J.: Brit. J. Surg. **33**:280, 1946.
66. Salvesen, H. A.: Acta med. scandinav. **86**:127, 1935.
67. Longcope, W. T., and Fisher, A. M.: J. Mt. Sinai Hosp. **8**:784, 1942.

sarcoidosis, in 6 of which there had been evidence of myocardial insufficiency during life. In a review of the literature, Johnson and Jason [68] found eight cases with involvement of the heart. A case was described by these authors in which nodules were prominent in the myocardium and less frequent in the epicardium and endocardium at postmortem examination. Abnormalities of rhythm were also mentioned by these observers. Scotti and McKeown [69] cited 13 cases in which involvement of the heart was noted at postmortem examination. In five of these, death was attributed primarily to sarcoidosis of the heart. They also pointed out that dilatation of the heart may result from extensive pulmonary involvement. More recently, Simpkins [70] described generalized sarcoidosis with massive involvement of the auriculoventricular bundle observed in a patient with a 15-year history of carotid sinus syncope. Recently, I studied two cases of sarcoidosis involving the heart in which Aschoff bodies were present.

Stomach.—Gore and McCarthy [71] described a 26-year-old man with sarcoidosis of the stomach; histologic examination of a regional lymph node after resection of the stomach confirmed the diagnosis. They stated that Dr. Fred Stewart had presented a similar case at a surgical-pathologic conference of the New York Laboratory Association in November, 1942. Guibert [72] described a 61-year-old woman with signs and symptoms of peptic ulcer, which was located on the lesser curvature by roentgenologic examination. The stomach was resected and showed granulomas in the base of the ulcer and the mucosa, without giant cells, caseation, or tubercle bacilli.

Intestine.—Watson and his co-workers [73] reported two cases of isolated sarcoidosis of the small intestine simulating regional ileitis and supposedly proved by histologic examination of the resected specimens. They reexamined 21 cases of regional ileitis, but sarcoid lesions were not found in any of the specimens. They concluded that sarcoidosis accounts for only a minor fraction of the cases of regional ileitis. Hadfield [74] stated that the epithelioid cell tubercles represented the specific lesion of regional ileitis. Thirteen of his 20 cases, he cautiously suggested, represented sarcoidosis. Morland [75] described a case of regional ileitis with sarcoidosis of the lung, seen on roentgenologic examination. On histologic examination the resected specimen and a mesenteric lymph node were described as appearing to be consistent with sarcoidosis. The tuberculin test, using 0.01 mg. of old tuberculin, was sharply positive, however. Snapper and Pompen [76] stated definitely that there was no relationship between regional ileitis and sarcoidosis. Warren and Sommers [77] rejected the idea that sarcoidosis and cicatrizing ileitis

68. Johnson, J. B., and Jason, R. S.: Am. Heart J. **27**:246, 1944.
69. Scotti, T. M., and McKeown, C. E.: Arch. Path. **46**:289, 1948.
70. Simpkins, S.: J. A. M. A. **146**:794, 1951.
71. Gore, I., and McCarthy, A. M.: Surgery **16**:865, 1944.
72. Guibert, H. L.: Ann. anat. path. **17**:295, 1947.
73. Watson, C. J.; Rigler, L. G.; Wangensteen, O. H., and McCartney, J. S.: Gastroenterology **4**:30, 1945.
74. Hadfield, G.: Lancet **2**:773, 1939.
75. Morland, A. A.: Tubercle **28**:32, 1947.
76. Snapper, I., and Pompen, A. W. M.: Besnier-Boeck's Disease: Visceral Localisation of the Sarcoids of Boeck, in Snapper, I.: Pseudo-Tuberculosis in Man, New York, Stechert-Hafner, Inc., 1938, pp. 1-34.
77. Warren, S., and Sommers, S. C.: Am. J. Path. **24**:475, 1948.

are the same disease. They stated that the granulomas of sarcoidosis are larger and lack the lymphocytic infiltration seen in cicatrizing ileitis, a point on which I disagree. It is of interest that in two of their three cases of regional ileitis observed at postmortem examination, there were granulomas in the liver.

Liver.—A true analysis of the incidence of hepatic involvement in cases of sarcoidosis is difficult. According to Reisner,[22] the liver and the spleen were more commonly involved than clinical examination would suggest. Freiman [13] thought that the liver was only slightly less frequently involved than the spleen. He noted the predilection of this disease for the portal triads, a characteristic which aids in differentiating it from miliary tuberculosis. Rosenthal and Feigin [78] reported four cases, with hepatic involvement in two. Rakov and Tayler [28] reported a case in which a definite diagnosis was made by liver biopsy. Baird and his associates [79] confirmed the diagnosis of sarcoidosis in three cases by liver biopsy. They thought this method was useful in the absence of cutaneous lesions and lymphadenopathy.

Kidney.—Renal involvement rarely is an important clinical observation in cases of sarcoidosis. The incidence of renal change at postmortem examination shows wide variation in different series. Freiman [13] stated that 20% of the cases of sarcoidosis seen at postmortem examination gave evidence of renal involvement. In six cases of sarcoidosis seen at postmortem examination, Nickerson [25] did not note renal involvement in a single instance. The kidney was implicated 7 times in the 29 cases reported by Friedman.[60] In Fisher's 94 cases,[11] the kidney apparently was involved in 5, but involvement was proved in only 3. Bates and Walsh [80] described seven patients, with a postmortem examination on one showing renal involvement. Klinefelter and Salley [81] reported a case of sarcoidosis with minimal urinary findings, azotemia, anemia, and normal blood pressure. They noted three other cases in an extensive review of the literature. Postmortem examination was performed in only one of these four cases, and in that instance renal involvement was demonstrated.

Bladder.—Redewill [82] suggested that malacoplakia is a form of sarcoidosis. He described one patient with generalized sarcoidosis who, at cystoscopy, was found to have malacoplakia. In malacoplakia, epithelioid cells arranged in the form of miliary tubercles are found, while inclusion bodies, called Michaelis-Gutmann bodies, are present in giant cells. Wells [83] thought these bodies were formed from urine extravasated into an edematous inflamed vesicle mucosa by slow diffusion. This question must be left unanswered at the present time, although it would appear that the two diseases are not related.

Central Nervous System.—Erickson and his associates [84] described a case in which sarcoidosis involving the central nervous system was demonstrated at postmortem examination. There was a "pressure cone," and collections of epithelioid cells, giant cells, and plasmacytes, arranged perivascularly, were found, particularly in the pia-arachnoid of the brain stem and the interpeduncular fossa. These

78. Rosenthal, J., and Feigin, I.: Arch. Path. **45**:681, 1948.
79. Baird, M. M.; Bogoch, A., and Fenwick, J. B.: Canad. M. A. J. **62**:562, 1950.
80. Bates, G. S., and Walsh, J. M.: Ann. Int. Med. **29**:306, 1948.
81. Klinefelter, H. F., Jr., and Salley, S. M.: Bull. Johns Hopkins Hosp. **79**:333, 1946.
82. Redewill, F. H.: J. Urol. **49**:401, 1943.
83. Wells, H. G.: Arch. Path. **26**:32, 1938.
84. Erickson, T. C.; Odom, G., and Stern, K.: Arch. Neurol. & Psychiat. **48**:613, 1942.

observers cited two other cases reported in the literature in which there was histologic confirmation of sarcoidosis of the central nervous system. Fisher [11] found 12 instances (13%) of involvement of the nervous system in his series. He stated that the most common result of involvement of the central nervous system was paralysis of one or both facial nerves, at times associated with involvement of the parotids. Roos [85] described eight patients with neurologic signs. In three of these, the disease was fatal, and basal lesions were seen histologically; the brain was involved in two, and the meninges in one.

Pituitary Gland.—The endocrine glands have been implicated occasionally in reports of sarcoidosis. Tillgren,[86] in 1935, described what was apparently the first case in which diabetes insipidus was a symptom of sarcoidosis. This case is hardly applicable, however, since it terminated in tuberculous peritonitis. Kraus [87] reported a case of sarcoidosis in which involvement of the pituitary, lungs, lymph nodes, liver, and spleen was seen at postmortem examination. In this case no significant pathogens which could be recovered from cultures or animal inoculations were demonstrated, including mycobacteria. The patient had hypoplasia of the genitals, polyuria, and an atrophic thyroid. Glass and Davis [88] discussed the case of a 54-year-old man who had granulomatous lesions in the pituitary, with failure of function in the thyroid, the adrenal cortices, and the testes. These authors thought differentiation between tuberculosis and sarcoidosis was not possible. However, in their case they demonstrated c. seation, tubercle bacilli in the sputum, and a positive Matoux test. Barber [89] described a patient who had low-grade cyclitis and loss of libido, sexual potency, body hair, and appetite, all of which were considered to be caused by sarcoidosis, although no histologic studies were made. Fisher [11] presented a case of sarcoidosis associated with diabetes insipidus; at postmortem examination the pituitary was shown to be largely replaced by sarcoid lesions. In two of Nickerson's cases,[25] sections of the pituitary were examined, and no sarcoidosis was reported.

Thyroid Gland.—Spencer and Warren [89] described what was apparently the first case of generalized sarcoidosis with involvement of the thyroid gland seen at postmortem examination. Cummins and his associates [90] reported a case in which a 25-year-old Negress was treated with propylthiouracil for hyperthyroidism and preoperatively with iodine, and underwent partial thyroidectomy. Microscopic examination revealed sarcoidosis.

Other Organs and Tissues.—Other organs or structures rarely are involved in sarcoidosis. In Nickerson's series,[25] the pancreas and the testes were involved in one case each. The nasal tissues or accessory air sinuses were involved in 6% of the cases reported by Fisher.[11] The tonsils were involved in 3 of Friedman's [60] 29 cases. Scandinavian reports frequently indicate a relatively high incidence of tonsillar involvement. The mucous membranes also are involved occasionally. The breast was mentioned as involved twice in Reisner's series.[28]

85. Roos, B.: Acta med. scandinav. **104**:123, 1940.
86. Tillgren, J.: Brit. J. Dermat. **47**:223, 1935.
87. Kraus, E. J.: J. Lab. & Clin. Med. **28**:140, 1942.
88. Glass, S. J., and Davis, D. S.: J. Clin. Endocrinol. **4**:489, 1944.
89. Spencer, J., and Warren, S.: Arch. Int. Med. **62**:285, 1938.
90. Cummins, S. D.; Clark, D. H., and Gandy, T. H.: A. M. A. Arch. Path. **51**:68, 1951.

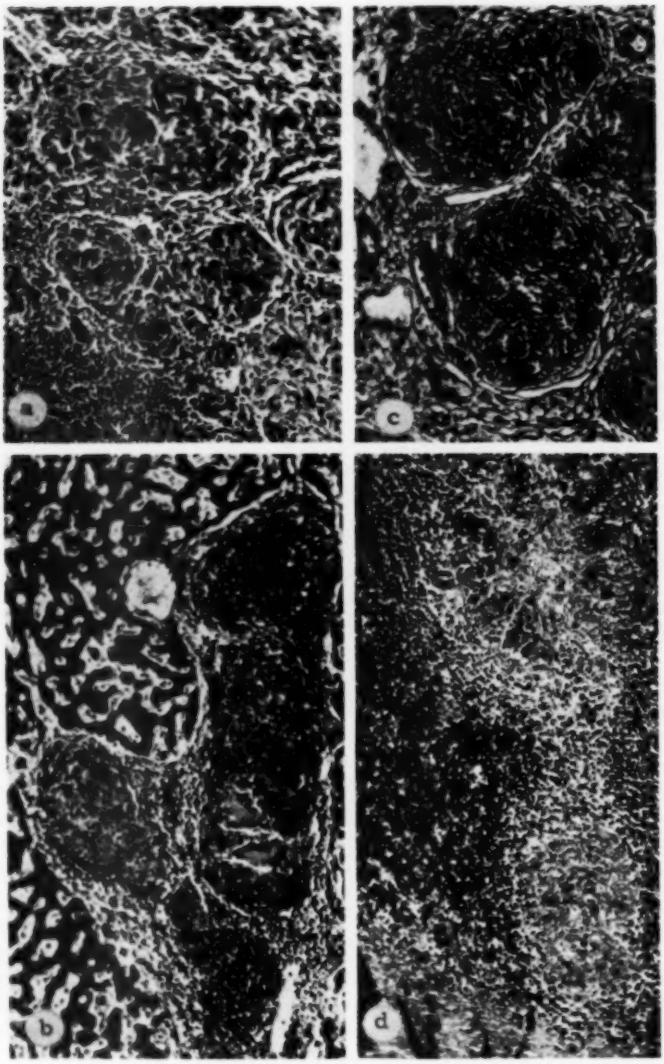

Fig. 1 (*a*) Lymph node. Numerous granulomas are dispersed throughout the node and frequently lie near the sinusoids. There is absence of necrosis. (Phloxine-methylene blue; × 120.) (*b*) Liver (Case 2). Five granulomas are present in the periportal area of a liver lobule. The granulomas are surrounded by numerous lymphocytes. (Phloxine-methylene blue; × 120.) (*c*) Lymph node. Concentric distribution of the reticulum is apparent peripherally, while centrally there is a radial arrangement of the fibrils. (Wilder's reticulum stain; × 120.) (*d*) Spleen (Case 2). Granulomas are present in the white pulp just beneath the capsule. These represent early healing as manifested by fibrosis, collagenization, and loss of cell detail. (Phloxine-methylene blue; × 120.)

HISTOLOGY

Histologically, the lesions are similar in all locations. The lesion is granulomatous and frequently has been referred to as a hard tubercle (Fig. 1*a*). It consists of focal aggregates of histiocytes which form epithelioid cells. Giant cells usually are present in the granulomas and are of the Langhans and foreign-body type. Lymphocytes generally are noted around the periphery of the granulomas. Nickerson [25] laid down a rigid set of histologic criteria that generally are accepted. He stated: 1. Caseation should never be present, although a fibrinoid material may be found. 2. The giant cells usually are larger than those in tuberculosis and contain more nuclei (25 to 30), which are evenly distributed. 3. The lesions do not contain carbon pigment in tissues other than the lungs. 4. In the liver, they are most common in the portal areas (Fig. 1*b*). 5. Silver impregnation always reveals a

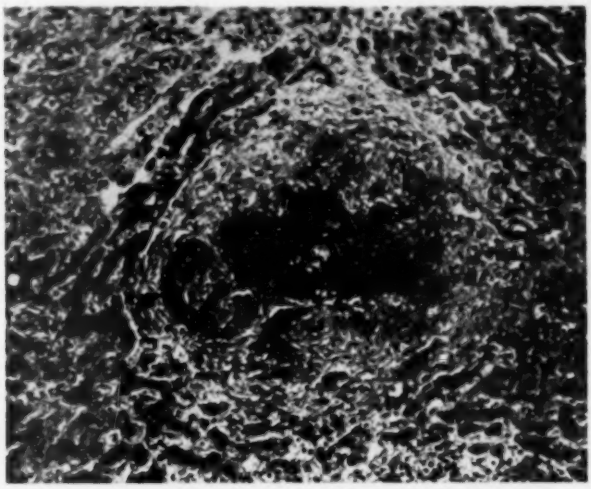

Fig. 2.—Liver (Case 2). The granuloma shows fibrinoid necrosis. Portions of two other granulomas can be seen, and a diffuse inflammatory cell infiltrate consisting of lymphocytes, plasmacytes, and a few eosinophiles is present between the lesions. (Phloxine-methylene blue; × 150.)

delicate reticulum to be present. 6. No evidence of tuberculosis can be found anywhere in the body. Nickerson stated further that eosinophiles are noted peripherally about the lesions, a point which Harrell [91] has denied. I agree with Nickerson that eosinophiles frequently are present in and about the granulomas. Teilum [92] and Bates and Walsh [80] stressed the finding of plasmacytes in and about the granulomas. Rakov and Tayler [38] stated that individual sarcoid nodules do not fuse to produce conglomerate sarcoid lesions, as is observed in tuberculosis. There is a reticulum network arranged concentrically at the periphery and radially in the central portion of the granulomas (Fig. 1*c*).

91. Harrell, G. T.: Arch. Int. Med. **65**:1003, 1940; footnote 36.
92. Teilum, G.: Am. J. Path. **24**:389, 1948.

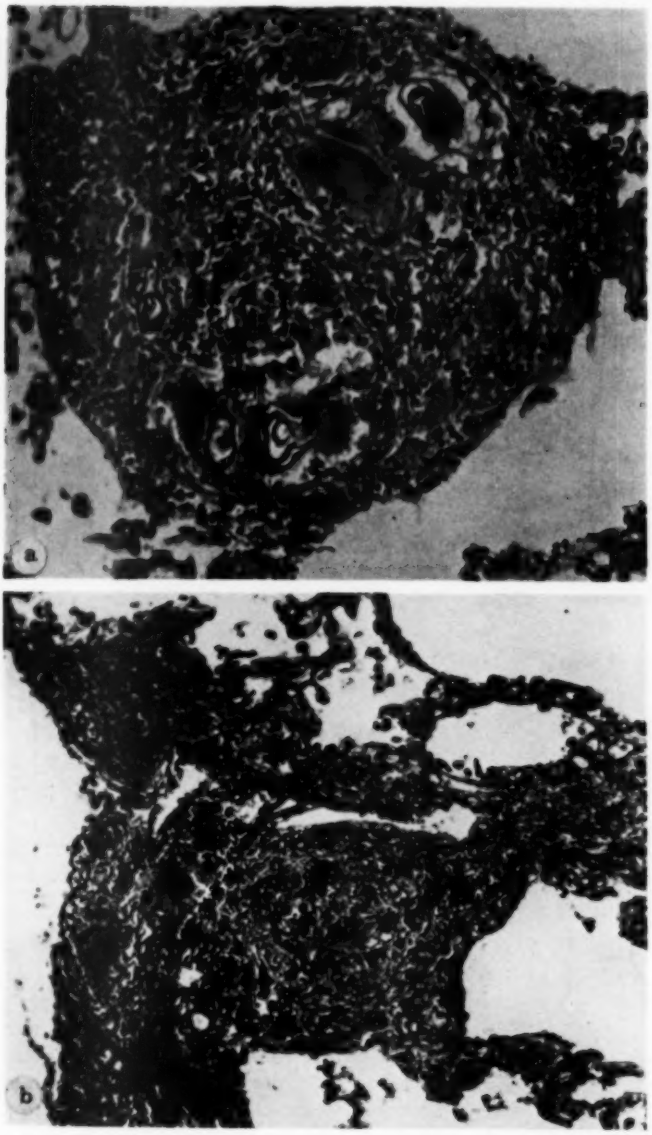

Fig. 3.—Lung: (*a*) Large granuloma in an alveolar septum. Four Schaumann bodies which display concentric lamellation can be seen in giant cells. Lymphocytes and plasmacytes surround, and to a lesser degree infiltrate, the granuloma. (Phloxine-methylene blue; × 180.) (*b*) The subpleural location of the granuloma is sharply defined. It is also in juxtaposition to a small blood vessel. An occasional lymphocyte can be seen in the granuloma, and a focal aggregate is apparent at the periphery. (Phloxine-methylene blue; × 150.)

Rosenthal and Feigin [78] stressed healing in their paper. These authors described four patients, in all of whom healing was noted. This was manifested by regression or fibrosis and hyalinization without calcification (Fig. 1*d*). Gore and McCarthy [71] stated that the fibrous tissue often stains for amyloid. Teilum [92] also stressed the fact that the connective tissue was similar to amyloid and called it paramyloid. Mallory [46] noted that frequently the lesions were surrounded by fibroblasts. In the older lesions, the fibroblasts were more numerous, and eventually the lesions were almost completely replaced by relatively acellular, whorled collagen. Frequently, acicular clefts were arranged in sheets, with parallel or slightly radiating long axes noted in the older lesions. He believed also that caseation necrosis does not occur, but that often "fibrinoid" necrosis can be seen (Fig. 2). Ricker and Clark [93] found this to occur in 35% of their cases. In referring to the pulmonary parenchyma,

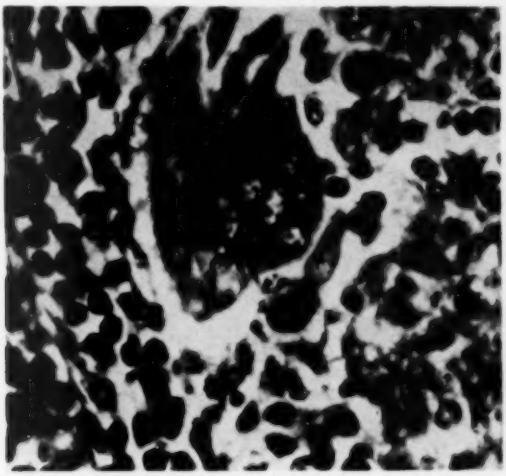

Fig. 4.—Spleen (Case 2). An asteroid body can be seen in a Langhans giant cell. The giant cell is at the periphery of a granuloma. The lesion is located in the white pulp. (Phloxine-methylene blue; × 800.)

they stressed the point that the lesions always appear to develop in the interstitial tissues and never in the alveoli or the air passages (Fig. 3*a* and *b*). In their patients, the oldest lesions were noted beneath the pleura and about blood vessels and bronchi, especially near the hilus. It should be emphasized that these granulomas have a close relationship to blood vessels and lymphatics in all viscera.

These lesions fail to reveal tubercle bacilli or any other parasitic organism by the usual bacterial stains. Usually, animal inoculation yields negative results. In many of the earlier reported cases the finding of tubercle bacilli in tissues or on animal inoculation and cultures was stressed. I believe that the finding of tubercle bacilli negates the diagnosis of sarcoidosis. This will be discussed at length under etiology.

93. Ricker, W., and Clark, M.: Am. J. Clin. Path. **19**:725, 1949

Hannesson [8] stated that the histologic picture described does not include the earliest phase of the lesion. This statement is true; there seems to be only one description of the earliest lesion in the literature. Ricker and Clark [93] described a "presarcoid" lesion of lymph nodes which consisted of a nonspecific proliferation of the littoral sinusoidal reticuloendothelium, which choked the lymphatic sinusoids,

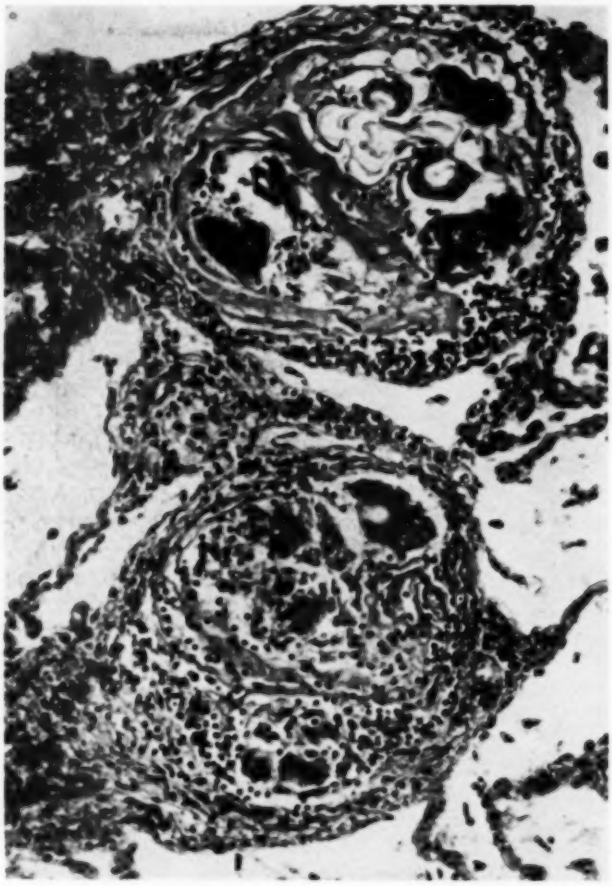

Fig. 5.—Lung (Case 1). Two large granulomas are present in the alveolar septums, with prominent Schaumann bodies and an asteroid body. The concentric lamellae of one Schaumann body are too large for a giant cell to contain. (Phloxine-methylene blue; × 180.)

while there was little reaction in the rest of the nodes. The earliest reported granulomas always occurred in juxtaposition to such a sinusoid.

Inclusion Bodies.—1. Asteroid Bodies: Inclusion bodies frequently are associated with sarcoidosis. They are of two types—asteroid bodies and Schaumann

bodies. The former were first described in 1890, by Goldmann,[94] in relation to a dermoid cyst. Wolbach,[95] in 1911, described five cases in which these inclusion bodies, associated with granulomas, were found in the lungs, hilar lymph nodes, spleen, liver, and lymph nodes of the neck and mesentery. Usually, they were in giant cells, and only rarely were they found free in the sinuses of the lymph nodes. The bodies were eosinophilic, with spinous processes radiating from a central spheroid body (Figs. 4, 5, and 6). The results of staining with scarlet red, osmic

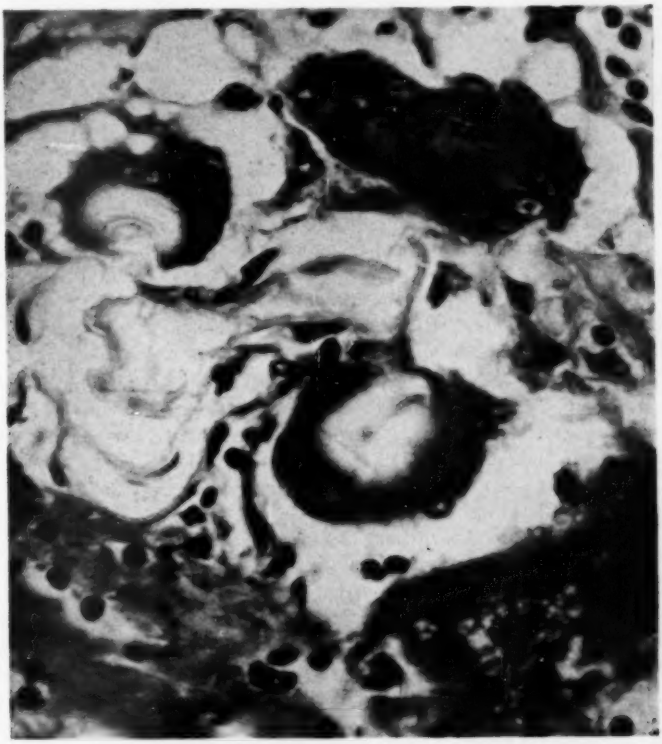

Fig. 6.—Lung (Case 1). Higher magnification of a part of Figure 5, depicting details of a Schaumann body and an asteroid body. The resemblance of the lamellae to chitinous material is more noticeable. (Phloxine-methylene blue; × 760.)

acid, iron-hematoxylin, or Weigert's elastic tissue stain and the iron reaction were negative. In one case there was a positive staining reaction for fibrin. According to Wolbach,[95] no satisfactory explanation was possible, and the cases described had nothing in common. In retrospect, all the cases fulfilled the criteria for sarcoidosis. Friedman [60] made an extensive study of asteroid bodies. He found that they failed to dissolve in water, alcohol, or xylene and did not dissolve or show morphologic

94. Goldmann, E. E.: Beitr. path. Anat. **7**:553, 1890.

95. Wolbach, S. B.: J. M. Res. **19**:243, 1911.

alterations when immersed in either a 1% solution of sodium hydroxide or a 10% solution of formic acid for 15 minutes. They stained pink with hematoxylin and eosin, gave negative staining reactions for collagen with phosphotungstic acid-hematoxylin, Mallory's aniline blue, Masson's trichrome, and hematoxylin and Van Gieson's stain, and gave negative reactions for reticulum and elastic tissue stains. He concluded that asteroids are stable chemically, respond negatively to the more common stains for specific substances, and exhibit approximately the same staining reactions as the cytoplasm of endothelioid or giant cells. The possibility of their being extraneous organisms could not be excluded, but it seemed doubtful. They did not exhibit the features of crystalline bodies. In no instances have Schaumann bodies been shown to change into stellate inclusions.

Hirsch [96] considered asteroid bodies to be crystalline forms of fat which had become altered in some way so that they were insoluble in fat solvents and gave some of the staining reactions of elastica. Lever and Freiman[97] stated that 68 cases of sarcoidosis with asteroids have been described in the literature; in 5 of these the lesions occurred in the skin. In their case they found asteroid bodies in 3% of the giant cells. Ricker and Clark [98] found asteroids in 2% of their cases.

Asteroid bodies certainly are not diagnostic of sarcoidosis, but they aid in the recognition of the disease. They have been described as occurring in torulosis by Stoddard and Cutler,[98] in leprosy by Mallory,[99] and in a probable case of Weber-Christian disease by Görl.[100] Ricker and Clark[98] noted their occurrence in tuberculosis, leprosy, histoplasmosis, schistosomiasis, and lipoid granuloma.

2. Schaumann Bodies. Schaumann [101] first described the inclusion bodies bearing his name in 1917. He reviewed the nature of these structures in 1941.[102] They vary considerably in size and form, the smallest assuming the size of a polymorphonuclear leukocyte and being round or oval in shape and surrounded by a membrane whose two contours stain strongly with polychrome blue and carbolthionine. They are doubly refractile (Figs. 3*a*, 5, 6, and 7*a*). As the body increases in size, the double contours are less distinct, and the formation appears to be composed of a number of concentric lamellae. Frequently they fill a giant cell, and they may burst these structures and lie in the intercellular spaces, with remnants of the giant cell close by. Lev and Hinkle [103] stated that they are found only in giant cells, a point which apparently is erroneous. They have been observed in practically all locations where lesions of sarcoidosis are found. They stain blue with hematoxylin and deep red by Unna's method. Frequently they stain preferentially with Weigert's elastic stain and von Kossa's stain. They are not acid-fast or stained by Gram's method.

96. Hirsch, E. F.: Arch. Path. **20**:665, 1935.

97. Lever, W. F., and Freiman, D. G.: Arch. Dermat. & Syph. **57**:639, 1948.

98. Stoddard, J. L., and Cutler, E. C.: Torula Infection in Man: A Group of Cases, Characterized by Chronic Lesions of the Central Nervous System, with Clinical Symptoms Suggestive of Cerebral Tumor, Produced by an Organism Belonging to the Torula Group (Torula Histolytica, N. Sp.), New York, Rockefeller Institute for Medical Research, 1916, p. 55.

99. Mallory, F. B.: The Principles of Pathologic Histology, Philadelphia, W. B. Saunders Company, 1914, pp. 207 and 613.

100. Görl, P.: Arch. Dermat. u. Syph. **148**:130, 1924.

101. Schaumann, J.: Ann. dermat. et syph. **6**:357, 1917.

102. Schaumann, J.: Acta med. scandinav. **106**:239, 1941.

103. Lev, M., and Hinkle, C. L.: Bull. U. S. Army M. Dept. **6**:617, 1946.

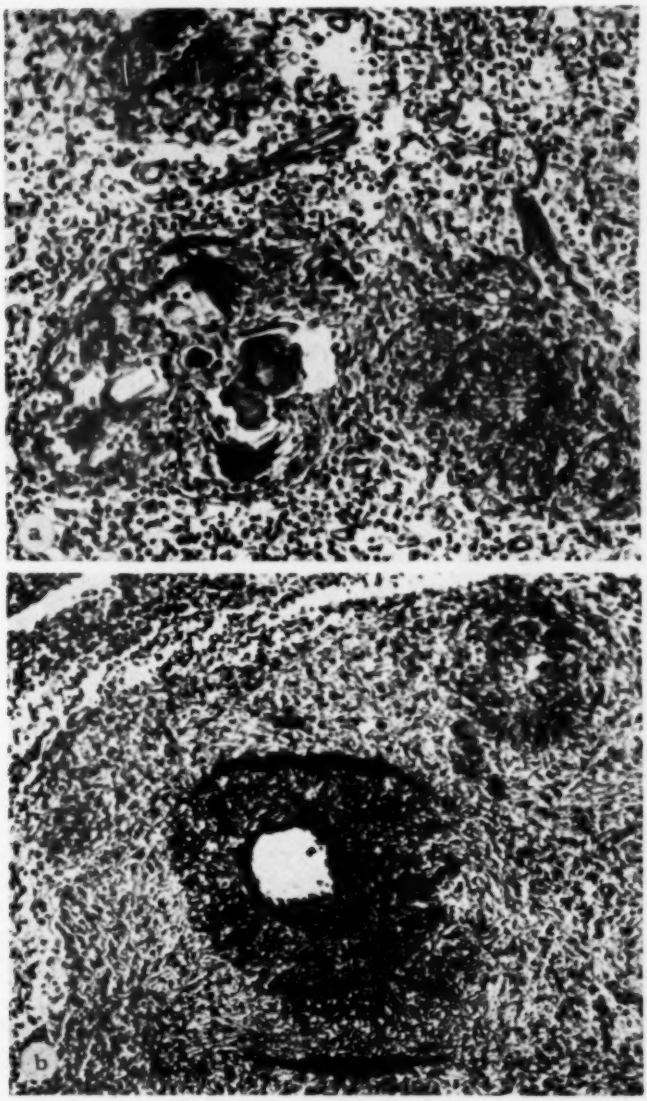

Fig. 7.—(*a*) Mesenteric lymph node (Case 2) with granulomas containing Schaumann bodies. These inclusions differ from the previous ones by being more dense and less distinctly lamellated and by varying markedly in size. (Phloxine-methylene blue; × 180.) (*b*) Mesenteric lymph node (Case 2). An arteriole displaying necrotizing arteriolitis can be seen, with an agglutinative thrombus. Granulomas can be observed surrounding the vessel and at a distance from it. (Phloxine-methylene blue; × 150.)

In their early stages, I have found that these bodies stain with the Hotchkiss-McManus preparation and do not take the stain for collagen.

The exact nature of these inclusion bodies is not known. Most authors consider them to be products of degeneration of elastic fibrils impregnated with calcium and iron. The interior of the bodies has been reported in the past to contain connective tissue,[101] hair,[104] tubercle bacilli,[105] and fungus elements.[101] Teilum[106] believed that the deep red staining by Unna's method was indicative of a content of ribose nucleotide, which is considered characteristic of protein formation and probably accounts for their basophilia. Furthermore, he thought that the stratified bodies were due to a biochemical (partly crystalline) precipitate, of the nature of a globulin, in the cytoplasm, where they behave like foreign bodies. The presence of plasmacytes in granulomas helps to substantiate Teilum's hypothesis. Skavlem and Ritterhoff [107] stated that Schaumann inclusion bodies occurred in 4% of the reported cases of sarcoidosis seen at postmortem examination. Riley [19] found them in 7 of 44 cases (16%) and stressed that they are seen also in leprosy, tuberculosis, and lupus erythematosus. Ricker and Clark [93] found Schaumann bodies in 3.6% of their cases and noted that they are found also in lymphogranuloma venereum and in lymph nodes draining areas of regional ileitis. Martland and his associates [108] and Grier and his co-workers [109] described inclusion bodies in the skin lesions of berylliosis, but their illustrations were not convincing.

Elsewhere in this issue of the ARCHIVES, Jaques,[110] describing a case of sarcoidosis, depicts a Schaumann body being formed from a nematode larva in the subcutaneous tissue of the perineum. This is believed to be the first description of the formation of these bodies. The connection between Schaumann bodies and asteroid bodies, if any, remains obscure.

RESULTS OF LABORATORY STUDIES

Sedimentation Rate.—Certain standard laboratory procedures are of great value in helping to substantiate the diagnosis of sarcoidosis. Frequently, hematologic examination reveals an elevated erythrocyte sedimentation rate, eosinophilia, relative monocytosis, or a combination of these. The erythrocyte sedimentation rate was elevated in five of seven cases reported by Bates and Walsh.[80] Bruce and Wassén [24] described 5 cases in which the erythrocyte sedimentation rate was elevated at some time during the disease. On the other hand, an accelerated erythrocyte sedimentation rate was present in only 3 of the 33 cases reported by Reisner.[23] Cone,[17] Stone,[28] and Rakov and Tayler [26] all stressed an elevated erythrocyte sedimentation rate. Ricker and Clark,[93] using the Cutler method, found that the erythrocyte

104. Lombardo, quoted by Schaumann.[102]

105. Metchnikoff, E.: Lectures on the Comparative Pathology of Inflammation, Delivered at the Pasteur Institute in 1891, Translated by F. A. Starling and E. H. Starling, London, Keegan, Paul, Trench, Trübner & Co., 1893, 218 pp.

106. Teilum, G.: Am. J. Path. **25**:85, 1949.

107. Skavlem, J. H., and Ritterhoff, R. J.: Am. J. Path. **22**:493, 1946.

108. Martland, H. S.; Brodkin, H. A., and Martland, H. S., Jr.: J. M. Soc. New Jersey **45**:5, 1948.

109. Grier, R. S.; Nash, P., and Freiman, D. G.: J. Indust. Hyg. & Toxicol. **30**:228, 1948.

110. Jaques, W. E.: Relationship of Nematode Larvae to Generalized Sarcoidosis; Report of a Case and Review of the Literature, Arch. Path., this issue, p. 550.

sedimentation rate was normal, 0 to 10 mm., in 38% of their cases, more than 11 mm. in 62%, and more than 30 mm. in 27%. Riley [19] found an elevated erythrocyte sedimentation rate in 78% of his cases.

Blood Changes.—Slight hypochromic microcytic anemia associated with sarcoidosis was mentioned by Stone [28] and Cone.[17] Mild leucopenia was noted by Cone,[17] and if it was marked, he considered that it suggested splenic involvement. A low or normal leucocyte count with neutropenia was mentioned by Rakov and Tayler.[38] Cone [17] noted eosinophilia in which the percentage of eosinophiles varied to as much as 35%, and he stated that this was considered by some as an index of activity. Reisner [23] found 6 to 14% eosinophiles in a fourth of his cases. Eleven per cent of the 94 patients described by Fisher [11] had eosinophilia. Harrell [91] observed the number of eosinophiles to be greater than 5% in 4 of his 11 cases. Others [111] have mentioned eosinophilia also. Relative monocytosis was noted by Cone,[17] Reisner,[23], Rakov and Tayler,[38] and Stone.[28] The number of monocytes ranged from 8 to 20% in half the cases reported by Reisner,[23] but it will be recalled that tuberculosis accounted for the majority of deaths in his series. Riley [19] found anemia in 25% of his cases, leucocytosis in 9%, leucopenia in 22%, eosinophilia in 24%, monocytosis in 16%, and granulocytopenia in 9%.

Serum Protein.—Harrell and Fisher [112] studied 11 patients who had sarcoidosis, diagnosed by biopsy of the skin or lymph nodes, and found the total protein to be more than 8 gm. per 100 cc. of serum in 8 of these. Harrell [91] described 7 of 11 patients in whom the total protein was greater than 7.5 gm. per 100 cc. of serum. Fisher and Davis [113] conducted extensive studies on the serum proteins of patients in various stages of the disease. In eight patients the total protein was greater than 8 gm. per 100 cc. of serum, and in seven of these eight, there was an increase in the gamma globulin accounting for 14 to 17% of the total protein. These authors studied four patients who had no clinical signs of activity of sarcoidosis; values for serum protein in these patients were almost normal, with only a slight decrease in values for serum albumin and a slight increase in those for gamma globulin. They concluded that the gamma globulin percentage is more consistently elevated in the active phase of sarcoidosis than is the total protein concentration. They further inferred that sarcoidosis is more likely to produce hyperglobulinemia and hyperproteinemia than is tuberculosis. Grekin and Curtis [114] found the value for total protein to be elevated in 3 and near the upper limits of normal in 4 of 12 cases studied, while the value for serum globulin was elevated in 5 and near the upper border of normal in 4 others. Fifty per cent of the 94 patients described by Fisher [11] had an elevated value for serum globulin. Ricker and Clark [93] examined 40 patients and found the value for serum protein to be greater than 8 gm. per 100 cc. of serum in nearly a third of them. The serum globulin was more than 3 gm. per 100 cc. in 60% of 31 cases examined. Riley [19] found an elevated value for serum globulin in 68% of his cases. Others [115] also have stressed the importance of hyperprotein-

111. Bruce and Wassén.[34] Stone.[28] Rakov and Tayler.[38] James and Wilson.[65] Bates and Walsh.[80] Tillgren.[86]

112. Harrell, G. T., and Fisher, S.: J. Clin. Invest. **18**:687, 1939.

113. Fisher, A. M., and Davis, B. D.: Bull. Johns Hopkins Hosp. **71**:364, 1942.

114. Grekin, R. H., and Curtis, A. C.: J. Invest. Dermat. **11**:299, 1948.

115. Cone.[17] Reisner.[23] Stone.[28] Rosenthal and Feigin.[78] Bates and Walsh.[80]

emia, hyperglobulinemia, and reversal of the albumin-globulin ratio. Harrell [91] and Harrell and Fisher [112] described small amounts of Bence Jones protein in two cases and stated that occasionally this protein is found in the absence of demonstrable bone lesions.

Serum Calcium, Phosphorus, and Alkaline Phosphatase.—Harrell and Fisher [112] observed an elevated value for serum calcium in 6 of 11 cases examined, and a normal value for serum phosphorus and an elevated value for alkaline phosphatase in every case in which these values were determined. Grekin and Curtis [114] found elevated values for serum calcium in 7 of 11 cases examined, elevated values for serum phosphorus in 5 of 11 cases, and normal values for alkaline phosphatase in all except one case, in which this enzyme was definitely elevated. Harrell [91] found the values for serum calcium to be greater than 10 mg. per 100 cc. in 9 of 11 cases. Cone [17] mentioned normal or slightly elevated values for serum calcium and elevated values for alkaline phosphatase. Riley [19] described elevated values for serum calcium in 18%, serum phosphorus in 18%, and alkaline phosphatase in 44% of his cases. Van Creveld [116] described a case of sarcoidosis in which there were hyperproteinemia, hypercalcemia, and, possibly, disturbed function of the parathyroid glands, but no good evidence for the diagnosis of sarcoidosis was presented. Schüpbach and Wernly [117] described three patients who had sarcoidosis with hypercalcemia, increased urinary calcium, and questionable hyperparathyroidism.

Miscellaneous Laboratory Procedures.—Cone [17] mentioned normal or slightly depressed levels of serum cholesterol in patients who had sarcoidosis. Harrell and Fisher [112] discussed impairment or slowing of hepatic function through abnormal excretion of bilirubin, fractional precipitation patterns of serum proteins, and an increase of serum alkaline phosphatase. Only one paper specifically mentioned that ova or parasites were not present in the stool. Apparently, evidences of parasitic infestation usually are not looked for in routine hospital examinations.

ETIOLOGY

In general, the cause of sarcoidosis is still unknown. Many etiologic agents have been suggested, but none has been established with certainty. The greatest controversy among students of this disease exists between the group which considers an anergic form of tuberculosis to be the responsible mechanism and the now larger group which denies that the causative agent is the tubercle bacillus. In this paper the etiologic agents will be described in the order suggested in the "Standard Nomenclature of Disease," published by the American Medical Association.

Brucella

Harrell [86] stated that patients who have sarcoidosis usually do not react to brucellergen. After extensive study of eight classic cases of sarcoidosis, Michelson [29] failed to find any relationship between this disease and brucellosis.

Mycobacteria

Mycobacterium Tuberculosis.—In a consideration of tuberculosis as an etiologic agent in sarcoidosis, the following points must be examined: (1) histologic appear-

116. van Creveld, S.: Ann. pædiat. **157**:1, 1941.

117. Schüpbach, A., and Wernly, M.: Acta med. scandinav. **115**:401, 1943.

ance, (2) the presence or absence of Myco. tuberculosis, (3) results of tuberculin skin tests, (4) association of sarcoidosis and tuberculosis, (5) results of serologic tests, (6) age distribution, and (7) organs involved.

1. Histologic Appearance: Superficially, the histologic features of sarcoidosis resemble those seen in tuberculosis, but there are subtle differences. The absence of caseation necrosis is stressed by most observers, although occasionally a report does mention caseation necrosis occurring in sarcoidosis.[19] On the other hand, fibrinoid necrosis frequently is encountered in the center of the granulomas of sarcoidosis. Silver impregnation reveals a delicate reticulum in the sarcoid lesions which, however, generally is present also in tuberculosis in the absence of caseation. Some authors [118] stress the observation that in tuberculosis the giant cells are larger and have more nuclei than those in sarcoidosis. Rakov and Tayler [38] noted that in sarcoidosis the epithelioid cells usually are larger and more cuboidal and that individual lesions do not conglomerate as they do in tuberculosis. Since superficially a similar histologic picture can be produced by a number of different agents, such as leprosy, syphilis, typhoid, lymphogranuloma venereum, tularemia, brucellosis, torulosis, Schistosoma mansoni infestation, and foreign bodies, no definite conclusions regarding the cause of sarcoidosis can be drawn from the histologic appearance alone.

2. Presence or Absence of Myco. Tuberculosis: The fact that tubercle bacilli have not been seen in the lesions of most authenticated cases of sarcoidosis is one of the major points used in negating tuberculosis as an etiologic agent. Ricker and Clark [92] studied 300 cases of proved sarcoidosis and found tubercle bacilli after guinea pig inoculation in 1 of 26 cases in which postmortem examination was performed. Cultures for tubercle bacilli were attempted in 36 cases, and guinea pig inoculations were made in 26 cases; 1 positive result was obtained by each method. Riley [19] used acid-fast stains on sputum and material obtained by gastric aspiration from 40 patients who had sarcoidosis; the results were positive in 4. Subsequently, smears and cultures of material from these four patients yielded negative results. Kyrle [119] found tubercle bacilli in a specimen 10 days after biopsy; 36 days after biopsy there were no tubercle bacilli, and on the 94th day the lesion had completely disappeared. The rapid course of the disease in this case was unlike that of sarcoidosis. Kyrle's patient probably had tuberculosis. Pautrier [118] stated that he never had found Myco. tuberculosis after inoculation of guinea pigs in any case of sarcoidosis which he had investigated personally. On the other hand, Pinner,[10] in a critical survey of the literature, found 25 cases of sarcoidosis in which tubercle bacilli were obtained.

Kyrle [119] stated that a foreign-body-type of response to the products of the disintegration of tubercle bacilli assumed the histopathologic picture of sarcoidosis. He postulated that tubercle bacilli were present in the early lesion but disappeared later. After reading the large amount of material available concerning sarcoidosis, one can conclude that in authenticated cases the finding of tubercle bacilli is a rare event. The incidence is similar to that found at random in a comparable group of

118. Pautrier, L. M.: Brit. J. Tuberc. **42**:1, 1948. Nickerson.[25]

119. Kyrle, J.: Vorlesungen über Histo-Biologie der menschlichen Haut und ihrer Erkrankungen, Berlin, Springer-Verlag, 1927, Vol. 2.

the general population. Certainly, the incidence would appear to be no greater than the coexistence of tuberculosis and Hodgkin's disease or bronchogenic carcinoma.

3. Results of Tuberculin Skin Tests: In most cases of sarcoidosis, negative results are obtained in tuberculin tests made with either old tuberculin or purified protein derivative, using doses as large as 1 mg. or its equivalent. It is best to consider the incidence of a positive tuberculin reaction in the population at large before drawing conclusions as to its incidence in patients having sarcoidosis.

Rich [120] tabulated the incidence of tuberculin reactors according to age and geographic location. In each case the final dose was not less than 1.0 mg. of old tuberculin or an equivalent amount of purified protein derivative. In rural Michigan the incidence of positive reactors was 6.1% among children from 0 to 5 years of age, 41.0% among persons 20 to 30 years old, and 76.4% among persons more than 40 years old. Among medical students entering the University of Pennsylvania the incidence of positive reactors was 85% in the 20- to 25-year group. The average incidence of positive reactions in 25 surveys was 60% in the 20- to 25-year group. This age range corresponds roughly to the ages having a peak incidence of sarcoidosis. Reisner [23] tested 25 patients who had sarcoidosis with 0.001 mg. of old tuberculin and obtained 1 positive reaction; among 33 patients who received 0.01 mg. of old tuberculin, 4 had positive reactions; among 29 who received 0.1 mg. of old tuberculin, 7 had positive reactions; among 23 who received 1.0 mg of old tuberculin, 2 had positive reactions, and among 10 who received 10.0 mg. of old tuberculin, none had positive reactions. Ricker and Clark [93] obtained 3 positive tuberculin reactions (3.4%) in 88 patients tested. Riley [19] gave the tuberculin test to 98% of his 52 patients who had sarcoidosis and found that 35% of those tested had positive reactions. Pautrier [118] obtained positive tuberculin reactions in a third of his patients. These and similar reports point to a lower incidence of positive tuberculin reactors among persons having sarcoidosis than in the general population. If the incidence of positive reactors among persons having sarcoidosis is compared with that among people in rural areas, the figures coincide more closely, although the incidence among people in rural areas still remains higher.

The lack of a positive tuberculin reaction in sarcoidosis has been attributed to anergy. If one considers the causes of a negative result of the tuberculin test, one finds that a negative result occurs (1) when the person tested has never had tuberculosis, (2) when tuberculosis is associated with cachexia, and (3) when other infectious diseases are present, such as scarlatina and, especially, rubeola. The latter two conditions are not pertinent in sarcoidosis.

Rich and McCordock [121] showed that in a variety of conditions allergy does not run parallel to immunity. If tuberculin is injected into normal (nontuberculous) guinea pigs, the tuberculin test at first is strongly positive and finally, in most animals, becomes completely negative. If virulent tubercle bacilli are injected after the test has become negative, no local or general reaction ensues. This sequence of events has been grasped by Freudenthal [122] as an explanation of the failure of patients having sarcoidosis to react positively to the tuberculin skin test.

120. Rich, A. R.: The Pathogenesis of Tuberculosis, Springfield, Ill., Charles C Thomas, Publisher, 1944.

121. Rich, A. R., and McCordock, H. A.: Bull. Johns Hopkins Hosp. **44**:273, 1929.

122. Freudenthal, W.: Brit. J. Tuberc. **42**:11, 1948.

Lemming [123] suggested that if patients who had sarcoidosis were absolutely anergic and therefore had not been infected earlier with tuberculosis, they should become tuberculin-positive after BCG vaccination. On the other hand, if positive anergy occurred, perhaps a somewhat different mode of reaction might be expected. He showed that in sarcoidosis tuberculin anergy is not generally influenced by BCG vaccination. However, in 3 of 11 previously reported cases a tuberculin allergy had been obtained.

4. Association of Sarcoidosis and Tuberculosis: In a case of sarcoidosis reported by Dorgeloh and Tully [124] there was tuberculosis in cervical lymph nodes but no cutaneous reaction to tuberculin. The nodes contained acid-fast bacilli, apparently having the same characteristics as tubercle bacilli, but no cultures of the organisms were made. Caseation necrosis was present.

Spiro [125] described a case of tuberculous infection evidenced by a few calcified nodes in the region of both hili of the lungs and a positive Pirquet reaction. Five years later, the lymph nodes became generally enlarged, and the disease was classified as sarcoidosis. The Pirquet test was positive during the illness but became negative after convalescence. Spiro thought this proved that sarcoidosis represents "tuberculosis in a 'positive' anergic subject with a raised degree of immunity."

That sarcoidosis terminated in active clinical tuberculosis was reported by Riley for 25% of his cases.[19] Three of 22 cases of sarcoidosis (13.6%) reported by Ricker and Clark [93] proved to be associated with tuberculosis at postmortem examination. In about 10% of the cases reported by Freiman [13] the sarcoidosis developed into active tuberculosis. This represents a higher percentage of tuberculosis than is described for most series. As noted previously, the incidence of overt tuberculosis probably is no greater in sarcoidosis than in other conditions, such as Hodgkin's disease and bronchogenic carcinoma.

5. Results of Serologic Tests: Pinner and his associates [126] considered "cutins" in relation to sarcoidosis. With appropriate mixtures of old tuberculin and serum, the skin reactivity is either enhanced (procutins) or decreased (anticutins). They thought that the high frequency of anergy to tuberculin in sarcoidosis was related to anticutins and that these substances were carried in the serum. Previously these authors had described three cases of sarcoidosis in which anticutins were demonstrated, and they added eight more cases, in one of which anticutins were present, a total of 4 out of 11 with anticutins (36%). They concluded that this subject must be left open for further study.

Antibodies to Myco. tuberculosis have been identified with considerable frequency in sera from patients having tuberculosis. It has been found that these antibodies can be detected in infected animals even when the the skin's sensitivity to tuberculosis has waned. Carnes and Raffel,[127] using the complement-fixation technic for the demonstration of antibodies, made immunologic comparisons between sarcoidosis and tuberculosis. Twenty-six cases of active tuberculosis, 30 cases in which there was a positive reaction to a first dose of purified protein derivative, and 29 cases in which there was a negative reaction to second-strength purified protein

123. Lemming, R.: Acta med. scandinav. **110**:151, 1942.
124. Dorgeloh, J. R., and Tully, P. W.: Arch. Path. **40**:309, 1945.
125. Spiro, P.: Ann. pædiat. **154**:199, 1939-1940.
126. Pinner, M.; Weiss, M., and Cohen, A. C.: Yale J. Biol. & Med. **15**:459, 1943.
127. Carnes, W. H., and Raffel, S.: Bull. Johns Hopkins Hosp. **85**:204, 1949.

derivative were selected for comparison. The complement-fixation technic showed antibodies to be present in 27.3% of the 22 patients who had sarcoidosis, in 61.7% of the 26 patients who had active tuberculosis, and in 33.3% of the 30 individuals who had given a positive reaction to the tuberculin test. There was no reaction in the 29 persons who had shown no reaction to the tuberculin test. This study revealed that the incidence of tuberculous infection demonstrated by the complement-fixation technic was higher than that demonstrated by cutaneous tuberculin reactivity. Eight of the 22 patients who had sarcoidosis had either a positive skin test or a positive complement-fixation test, which suggested that they might have had a tuberculous infection in the past, a not unreasonable possibility in this group. The belief that sarcoidosis bears an etiologic relationship to tuberculosis received no support from this study. Clinically and histologically the lesions of sarcoidosis were active, and yet in only 27.3% of the cases were antibodies demonstrated by complement fixation, and even in those the titers were lower than they were in the other groups.

6. Age Distribution: The incidence of tuberculosis increases with age. This is demonstrated by tuberculin testing, as previously noted, by case histories, and by roentgenologic surveys. On the other hand, most reports of sarcoidosis stress the high percentage of cases among young adults. Only rare cases of sarcoidosis are reported in childhood and old age, while tuberculosis is a common disease in both age groups.

7. Organs Involved: The organs involved in sarcoidosis and in tuberculosis are the same in some instances; for example, lungs, spleen, liver, lymph nodes, and bone marrow. There are differences, however. The incidence of myocardial involvement is much higher in sarcoidosis than in tuberculosis. Likewise, involvement of the uveal tract and parotid gland is much higher in sarcoidosis. Rich [129] pointed out that the lungs may be peppered with miliary sarcoid nodules, with practically no involvement of the spleen and the liver, a condition never seen in tuberculosis.

Brooke and Day [128] chose seven patients having sarcoidosis, proved by biopsy, whose sputum was negative for tubercle bacilli even on direct smear and culture. Eighteen mycobacterial tuberculins and one control preparation were tested in these seven individuals and in five healthy controls. It was observed that the patients who had sarcoidosis did not differ significantly from the normal controls in their response. The study was considered to be evidence against a tuberculous origin of sarcoidosis.

In summary I feel that there is not adequate evidence to permit the conclusion that tuberculosis is an etiologic factor in sarcoidosis. In fact, there appears to be evidence against this conclusion. The lack of demonstrable tubercle bacilli, except in equivocal cases, would seem to be the strongest evidence against the theory that tuberculosis is a cause of sarcoidosis.

Other Mycobacteria.—Rabello [129] found that the lesions of cutaneous and osseous sarcoidosis resembled leprosy, and he suggested this as a possible cause. Harrell and Horne [130] studied patients who had sarcoidosis for lepromin reaction. They

128. Brooke, W. S., and Day, R.: Bull. Johns Hopkins Hosp. **72**:101, 1943.

129. Rabello, J.: Ann. dermat. et syph. **7**:571, 1936.

130. Harrell, G. T., and Horne, S. F.: Am. J. Trop. Med. **25**:523, 1945.

found the reactions to be infrequent and slight, and no indication that sarcoidosis is atypical tuberculoid leprosy was found. They considered slight lepromin reactions to be of doubtful significance. Pautrier [118] stated that even if leprosy can be considered in the etiology of sarcoidosis in Brazil, "it is inconsistent that the same explanation can hold for European cases, which are common where leprosy does not occur." Cone [17] mentioned a mycobacterium between Myco. tuberculosis and Myco. leprae, or a pleomorphic variant, in his discussion of the etiology of sarcoidosis. It seems implausible that leprosy plays any part in causing this disease. The geographic distribution, the incidence of the two diseases, and the lack of intracellular organisms of appropriate morphologic and staining characteristics help to dismiss this from etiologic consideration.

Treponema Pallidum

Frazier and Hu [131] suggested syphilis as causative of sarcoidosis. This same disease was mentioned by Cone [17] and Stone [28] in their discussions of cause. The absence of positive results of serologic tests for syphilis, the failure to elicit a history of contact, the histologic appearance of the lesions of sarcoidosis, and the failure to demonstrate T. pallidum in tissue sections all serve to dismiss the idea that syphilis is responsible for sarcoidosis. Levitt [132] mentioned yaws in a discussion of cause, but this can be dismissed for similar reason.

Protozoa

Leishmaniasis has been mentioned as an etiologic factor of sarcoidosis by some observers.[133] The grounds for postulating that this disease may cause sarcoidosis are the similarity in histologic appearance and the hyperglobulinemia characteristic of both diseases. This suggestion, however, can be dismissed quickly, since the geographic locations of the two diseases do not coincide, and intracellular organisms of the type noted in leishmaniasis are not found in sarcoidosis.

Virus

In 1932, Kissmeyer [134] prepared an antigen from cutaneous lesions of sarcoidosis which was said to evoke a specific skin reaction. His method of preparation suggested the presence of a virus. The Kveim test [135] was devised to show whether a patient with sarcoidosis reacts to an antigen from sarcoid tissue of lymph nodes ground and suspended in a 0.5% solution of phenol. A patient suspected of having sarcoidosis received an intracutaneous injection of 0.1 to 0.2 cc. of the preparation. Local bluish-brown or bluish-red infiltrations appeared in one to four weeks. In some cases these resembled nodules of sarcoidosis histologically. No reaction was noted in the controls. Kveim thought the result was a specific allergic reaction to a specific virus.[135] Williams and Nickerson [136] postulated that sarcoidosis, like lymphogranuloma venereum, is a virus disease and that, as in the latter disease, an antigen could be formed from infected material and used for diagnostic purposes.

131. Frazier, C. N., and Hu, C. K.: Proc. Soc. Exper. Biol. & Med. **30**:898, 1933.
132. Levitt, J. M.: Arch. Ophth. **26**:358, 1941.
133. Stone,[28] Tice and Sweany.[45]
134. Kissmeyer, A.: La maladie de Boeck: Sarcoides cutanées bénignes multiples, Copenhagen, Ejnar Munksgaards Forlag, 1932, 147 pp.
135. Kveim, A.: Nord. med. **9**:169, 1941.
136. Williams, R. H., and Nickerson, D. A.: Proc. Soc. Exper. Biol. & Med. **33**:403, 1935.

Involved tissue removed from a patient with proved sarcoidosis was ground in sand, saline solution was added, and the material was sterilized at 60 C. for two hours on two consecutive days. Results of aerobic and anaerobic cultures were negative after 48 hours. Four patients who had proved sarcoidosis and four normal individuals received intradermal injections of the antigen. A skin reaction was produced in the patients having sarcoidosis but not in the controls. These observers thought that their findings suggested a virus disease and that it was possible to prepare a diagnostic serum. Warfvinge [137] thought that the test material might contain atypical and avirulent tubercle bacilli. Pautrier [118] considered the Kveim reaction to favor a virus theory, but he stated that a positive skin reaction also could be obtained from an antigen prepared from the lymph nodes of leukemic patients. He concluded that patients who have sarcoidosis give local sarcoid reaction in response to various substances. Harrell [91] prepared an antigen from a lymph node of a patient which caused a questionable positive reaction when injected intradermally into three patients who had sarcoidosis but no reaction in four controls. An antigen prepared from two other patients who had sarcoidosis gave a negative intradermal reaction in four other patients who had sarcoidosis and a questionable positive reaction when injected intradermally into the two patients from whom the extract was obtained.

Harrell [36] found that results of the Frei test for lymphogranuloma venereum were negative for patients suffering from sarcoidosis.

Fungi

Fungi have been implicated as a cause of sarcoidosis. Many early Scandinavian workers stressed the relationship of sarcoidosis and streptothrix, especially in regard to tonsillar lesions. Streptothrix is such a common contaminant that it is unlikely it plays any part in causing sarcoidosis. Longcope and Pierson [138] failed to grow fungi from the lesions of sarcoidosis on Sabouraud's medium.

Harrell [91] found that agglutination by blood serum of Candida albicans and complement fixation with blastomycetes antigen were absent in seven cases of sarcoidosis.

Helminths

The relationship of helminths to sarcoidosis is described elsewhere in this issue of the Archives by Jaques.[119] A case of sarcoidosis is presented in which larvae of Strongyloides stercoralis were tentatively identified in the subcutaneous tissues of the perineum. It was possible to demonstrate a Schaumann body being formed from these larvae.

In geographic distribution,[34] epidemiology,[34] racial predilection,[84] age of patients,[139] organs involved,[140] and results of laboratory studies, sarcoidosis and nematode infestation are similar. Hypersensitivity to the various antigenic princi-

137. Warfvinge, L. E.: Acta med. scandinav. **114**:259, 1943.

138. Longcope, W. T., and Pierson, J. W.: Bull. Johns Hopkins Hosp. **60**:223, 1937.

139. Girges, R.: J. Trop. Med. **37**:162, 1934.

140. Witenberg, G.: Acta med. orient. **4**:363, 1945. Suyemori, S.: Taiwan Igakkai Zasski **1**:239, 1925. Calhoun, F. P.: Arch. Ophth. **18**:963, 1937. Boettiger, C., and Werne, J.: J. A. M. A. **93**:32, 1929. Kyle, L. H.; McKay, D. G., and Sparling, H. J., Jr.: Ann. Int. Med. **29**:1014, 1948.

ples of nematodes [141] has been demonstrated adequately, and difference in histologic response of immune and nonimmune guinea pigs has been shown.[141a] The tissue reaction to larvae of Ascaris lumbricoides in the immune animal is granulomatous. It has been shown also that these granulomas are not always intimately associated with the larvae.[142]

The following report presents another case of sarcoidosis in which chitinous material resembling remnants of larvae were found in the lung.

CASE I.—A 64-year-old white man was admitted to the Massachusetts Memorial Hospitals, Boston, because of increasing paroxysmal nocturnal dyspnea of two years' duration. Two years previous to admission, exertional dyspnea and mild orthopnea had been noted, but there had been no ankle edema or chest pain. At the time of admission the heart was enlarged to percussion and displayed sinus arrhythmia, a Grade 3 systolic murmur over the aortic area, and a blowing diastolic murmur over the third interspace, to the right of the sternum. The blood pressure fluctuated between 155 and 120 mm. of mercury systolic and between 70 and 50 diastolic. Roentgenograms displayed dense calcification of the aortic ring and enlargement of the left atrium and ventricle. The patient was given digitalis and mercurial diuretics, but died suddenly during a severe coughing spell.

At postmortem examination, the heart weighed 720 gm., and the aortic valve displayed exuberant calcification, which extended from the base to the free margin, producing a triangular stenotic aperture. Over the posterior surface of the left ventricle near the apex was an area of myocardial scarring, 3 cm. in diameter. The lungs weighed 1,300 gm. and exuded copious amounts of pink, frothy fluid when squeezed. The spleen weighed 315 gm. and was not remarkable grossly. The liver weighed 1,350 gm. and revealed a firm, white capsule measuring 0.7 cm. in thickness and an indistinct lobular pattern on the cut surface. The prostate weighed 60 gm. and was grossly nodular. The only other positive gross observations were bilateral hydrothorax, generalized mild atherosclerosis, and Meckel's diverticulum.

Microscopically, granulomas were noted in the lungs, the spleen, the liver, lymph nodes, and the thyroid capsule. In the lungs, the granulomas were located in the interstitial tissues, the pleura, and the alveolar and interlobular septums. Generally, they were perivascular in distribution. They were composed of epithelioid cells and Langhans' and foreign-body-type giant cells, and they were surrounded by lymphocytes and a few plasmacytes. No fibrinoid or caseation necrosis was apparent. Schaumann bodies were associated with many of the granulomas (Figs. 3*a*, 5, and 6). These bodies were concentrically lamellated and were within the cytoplasm of giant cells. Frequently, the body was too large for a giant cell to accommodate, and a large portion of it was extracellular. The bodies were composed of from two to six lamellae which had a distinctly yellowish tint. Occasionally, a central basophilic mass was noted. The von Kossa and Hotchkiss-McManus stains failed to stain the bodies preferentially. Weigert's elastic tissue stain revealed central black bodies and concentric yellowish lamellae. With Ziehl-Neelsen preparation, the bodies remained yellow, with slight eosinophilia. No tubercle bacilli were demonstrated. The Schaumann bodies displayed a great likeness to chitinous material. No mention of nematode infestation was made. It can only be conjectured that these bodies may have been the remnants of parasites. Asteroid bodies also were encountered frequently, and it was common to find asteroid bodies and Schaumann bodies existing side by side (Figs. 5 and 6). Occasionally the granulomas revealed fibrosis and early collagen deposition.

In the liver the granulomas were located in the periportal areas and occasionally were hyalinized. These granulomas, as well as those in the spleen, lymph nodes, and the capsule of

141 (*a*) Kerr, K. B.: Am. J. Hyg. **27**:28, 1938. (*b*) Einhorn, N. H.; Miller, J. F., and Whittier, L.: Am. J. Dis. Child. **69**:237, 1945. (*c*) Jones, T. L., and Kingscote, A. A.: Am. J. Hyg. **22**:406, 1935. (*d*) Brunner, M.: Altman, I., and Bowman, K.: J. Allergy **15**:2, 1944. (*e*) Davidson, A. G.; Baron, B., and Walzer, M.: Ibid. **18**:359, 1947. (*f*) Rocha e Silva, M., and Graña, R.: Arch. Surg. **52**:523, 1946. (*g*) Oliver-González, J.: J. Infect. Dis. **72**:202, 1943. (*h*) Campbell, D. H.: Ibid. **59**:266, 1936.

142. Blackie, W. K.: J. Helminthol. **8**:93, 1930.

the thyroid, were not associated with inclusion bodies. It was interesting to note that sections of the heart displayed a few areas of fibrinoid necrosis and an occasional Aschoff body.

Two other cases of sarcoidosis have been reviewed recently. Granulomas were present in the liver in the first case and in the gastrocnemius muscle in the second. In the first case the granulomas were associated with material interpreted as representing larval remnants which formed Schaumann bodies in the portal triads. This makes a total of four cases of sarcoidosis in which the larvae of nematodes have been tentatively identified.

Beryllium

In recent years a few observers have suggested beryllium phosphors as being responsible for sarcoidosis. Higgins [143] described 35 patients who had pulmonary sarcoidosis, 30 of whom were employees in one industrial plant. All but 2 of the 35 were engaged in the manufacture of fluorescent lamps. He concluded that sarcoidosis might be due to beryllium because it occurred in persons employed in industries using beryllium. Jones [144] suggested that many cases are due to chronic beryllium granulomatosis. Other observers [145] have mentioned the similarity between the histologic pictures of berylliosis and sarcoidosis.

Foreign Bodies

Refvem,[146] using polarized light, examined tissue from 100 patients who had sarcoidosis. He noted that a few specimens contained refractile material; in one instance this was determined to be calcareous spar. He postulated that these particles might be responsible for a limited number of cases of sarcoidosis, since extremely small quantities might easily be overlooked on microscopic examination.

Calcareous spar is found in the soil of Cambrosilurian regions, and since sarcoidosis is more prevalent in rural areas, especially among farmers and gardeners, this was considered to be a possible etiologic element. Refvem further suggested that the spars, which are only a few microns in size, might be whirled up in dust and inhaled. Lime fertilizers and limestone might be inhaled, also. These compounds could enter the lymphatics and blood vessels to produce a generalized disease. Finally, the material might be removed, dissolved, or converted into amorphous, noninjurious compounds, which could explain remission of sarcoidosis in some instances.

German [147] reported the case of a man with a lacerated scalp in which débridement of small particles of stone was carried out. Years later, the scar became painful, and a nodule was excised. Whorls of epithelioid cells and giant cells were encountered, which contained clear, irregularly formed, nonstaining crystals. He suggested that this might be a sarcoid lesion, but it certainly was a nonspecific foreign-body reaction.

King [148] reported five cases of post-traumatic sarcoid lesions in which needle-shaped crystals were noted microscopically. The amount of crystalline material

143. Higgins, H. L.: Connecticut M. J. **11**:330, 1947.

144. Jones, C. M.: Tr. Am. Climatol. & Clin. A. **59**:70, 1947.

145. Martland and others.[108] Grier and others.[109]

146. Refvem, O.: Acta path. et microbiol. scandinav. **25**:107, 1948.

147. German, W. M.: Am. J. Clin. Path. **10**:245, 1940.

148. King, C. O.: South. M. J. **39**:122, 1946.

was too small for microincineration, but it was considered to be silica. They reported another case in which a sarcoid configuration occurred three months after a prick by a thorn bush. Again, these cases probably represent a granulomatous response to a nonspecific foreign body.

Tice and Sweany [45] suggested foreign bodies such as paraffin and petrolatum in their etiologic discussion.

Arteriolar Lesions

In recent years, isolated case reports mentioning the occurrence of arteriolar lesions and hyperergic states have appeared. Staehelin [149] described a 20-year-old girl who died after a two month history of lupus nasi and polyneuritis. At postmortem examination, a peculiar granulomatous process extended from the nasal septum to the dura mater, over the cerebrum. Histologic examination revealed a granulomatous lesion that resembled sarcoidosis but was modified by vascular lesions like those of periarteritis nodosa. In 1944, Gartside [150] described swelling of 11 years' duration in the submaxillary region in a 35-year-old man. Histologic examination of the tissue revealed a granulomatous lesion which had extended to the walls of small arteries in the inflamed tissue. The picture resembled giant cell arteritis but was not believed to be such. Gartside stated that it resembled the lesion following implantation of collagen in the rabbit, described by Pullinger and Pirie.[151] More recently, Teilum [92] suggested that a hyperergic state is concerned in sarcoidosis. In the following case of sarcoidosis, arteriolar changes were present in the liver, the kidneys, and a mesenteric lymph node.

Case 2.—A 73-year-old Negro woman was admitted to the Massachusetts Memorial Hospitals because of pain in the left chest and the left arm of three weeks' duration. She was known to have had diabetes for nine years. Multiple joint pains and swelling of the joints had been present for many years. Three weeks prior to admission a sharp, constricting pain was noted in the lower left portion of the chest. It was relieved by the administration of aluminum hydroxide gel U. S. P. and belladonna. The pain extended down the inner aspect of the left arm and was not relieved by administration of glyceryl trinitrate U. S. P. On physical examination she appeared chronically ill, with no rash or significant lymphadenopathy. The blood pressure was 180 mm. of mercury systolic and 100 diastolic, and there was a Grade 1 systolic murmur at the apex with a Grade 2 blowing murmur in the left second and third interspaces. The heart was enlarged to the left anterior axillary line. A few moist *râles* were present in the lungs. Hypertrophic arthritis was noted in the larger joints. The leucocyte count was 7,400, with 80% polymorphonuclear granulocytes, 12% lymphocytes, and 8% monocytes. The results of other laboratory procedures were essentially normal; no serum protein determinations were made. The day after admission the patient was given a transfusion, and five minutes after discontinuation she sat up, gasped, and died.

At postmortem examination, there was slight bilateral hydrothorax, and easily lysed fibrous adhesions were present at the apices of the lungs. The heart weighed 480 gm. and displayed a diffuse gray-white scarring of the left ventricular myocardium and interventricular septum. The coronary arteries were tortuous, with marked atheromatous beading and extensive calcification of the proximal few centimeters. The lungs were dry and revealed only atheromatous plaques of the pulmonary arteries. There was no hilar lymphadenopathy. The spleen weighed 230 gm. and was not remarkable grossly. There were numerous polyps in the gastric antrum and body and along the greater curvature. The right kidney weighed 110 gm., and the left, 160

149. Staehelin, H. R.: Arch. path. Anat. **309**:235, 1942.

150. Gartside, I. B.: J. Path. & Bact. **56**:61, 1944.

151. Pullinger, B. D., and Pirie, A.: J. Path. & Bact. **54**:341, 1942.

gm. The external surfaces were finely granular, and on coronal section a yellowish-white, circumscribed, slightly elevated area was noted in the left kidney. The thyroid weighed 30 gm. and exhibited a colloid adenoma, 0.6 cm. in diameter.

Microscopically, granulomas were noted in the lungs, lymph nodes, spleen, liver, bone marrow, and thyroid capsule. In the lungs, the granulomas were located in the pleura and the interlobular and alveolar septums, and peribronchially. Typical granulomas composed of histiocytes and giant cells were encountered; in other instances, only two to three giant cells, frequently containing asteroid bodies, were noted. At times, partial to complete hyalinization of the granulomas was observed. In the spleen, the granulomas were largely limited to the white pulp and frequently showed varying stages of healing (Fig. 1*d*). Asteroid bodies were noted in many giant cells (Fig. 4). Occasionally, single giant cells, with or without asteroid bodies, were dispersed throughout the splenic pulp. The granulomas of the liver were predominantly periportal in distribution (Fig. 1*b*), while one large subcapsular zone of granulomatous inflammation which extended into a thickened capsule was noted. In many areas the granulomas were associated with infiltration of lymphocytes, plasmacytes, and eosinophiles. Frequently, fibrinoid necrosis was present in the granulomas (Fig. 2). Occasionally, asteroid bodies were noted. Sections of kidney revealed intramural glomerulonephrosis, while one section displayed a wedge-shaped cortical zone of granulomatous inflammation with distinct fibrinoid necrosis. Necrotizing arteriolitis was noted in the prearterioles in this portion of the kidney. One section of a mesenteric lymph node showed granulomas displaying fibrinoid necrosis and containing numerous Schaumann bodies. These bodies presented a histologic appearance which differed from that in Case I. They were more solid, possessed less distinct lamellations, and varied considerably in size. They took on a deep red color with Ziehl-Neelsen staining (Fig. 7*a*). Necrotizing arteriolitis was noted in a few arterioles of the node (Fig. 7*b*). The granulomas in the vertebral bone marrow were sparsely distributed, and rare giant cells contained asteroid bodies. Sections of heart revealed a focal perivascular infiltration of eosinophiles, lymphocytes, and histiocytes, but no granulomas were noted.

This case demonstrates necrotizing arteriolitis occurring with sarcoidosis. I feel that it represents another hyperergic manifestation of the disease.

Neoplasms

In 1938, Scott [16] stated that the suggestion that sarcoidosis falls in the same category as leucosis and Hodgkin's disease seemed to be gaining increasing favor. The possibility that sarcoidosis may be neoplastic in origin was considered by Stone [29] in 1946. In 1950, Gherardi [152] presented a case of carcinoma of the common hepatic duct in which histologic examination of a regional lymph node revealed confluent granulomas of fairly uniform size. The patient died, and no granulomas were found in any of the other abdominal viscera. The author considered this to represent sarcoidosis. It would seem more likely that it was an example of the presence of local sarcoid lesions.

Nadel and Ackerman [153] described five cases of carcinoma (involving the oral cavity, skin, the breast, the ampulla of Vater, and the bronchus) in which histologic examination of the regional lymph nodes revealed sarcoid lesions. Tubercle bacilli were absent. In one case, Schaumann bodies were present, but no asteroid bodies were encountered. Likewise, Symmers [154] presented five cases of carcinoma (two involving the breast, one the thyroid, and two the bronchus) in which the regional lymph nodes displayed sarcoid-like lesions. Asteroid bodies were present in four of these cases. Symmers believed that the change represented a reaction to irritant

152. Gherardi, G. J.: Arch. Path. **49**:163, 1950.

153. Nadel, E. N., and Ackerman, L. V.: Am. J. Clin. Path. **20**:952, 1950.

154. Symmers, W. S. C.: Am. J. Path. **27**:493, 1951.

material, probably of lipoid or lipoprotein nature, produced in the tissues drained by the affected lymphoid tissue. He concluded also that the picture represented sarcoid lesions rather than sarcoidosis.

COMMENT

Heretofore, granulomatous lesions that could not be catalogued specifically frequently have been classified as "sarcoidosis." The first group that should be separated in all instances is the group of granulomas caused by tuberculosis. The presence of tubercle bacilli should be ascertained by culture, guinea pig inoculation, and Ziehl-Neelsen stains of histologic preparations. If they are found, the lesions should not be classified as sarcoidosis even though the histologic appearance suggests this disease. Likewise, the presence of caseation necrosis should negate the diagnosis of sarcoidosis.

As further knowledge is amassed, other granulomas can be taken out of the category of sarcoidosis and set in their correct place. Talc, beryllium phosphors, silicates, and other foreign bodies elicit a granulomatous reaction, and in some instances these reactions have been referred to as "sarcoidosis." These specific granulomas should not be considered as sarcoidosis.

The cases of sarcoidosis recorded in the literature can be divided into two main types—generalized sarcoidosis and focal sarcoid lesions. This differentiation has been stressed by other observers.[155] Frequently, sarcoid lesions are found at postmortem examination and in surgical specimens. They are particularly prevalent in the hilus of the lung and in lymph nodes. Their etiologic factors are obscure, although it it conjectured that a hyperergic response of the tissues, provoked by some as yet unidentified etiologic agent, may be responsible.

It is postulated that a nematode infestation may be responsible for some cases of sarcoidosis. The evidence in favor of this hypothesis has been presented, and it is hoped that this will stimulate further investigation along this line. In rural distribution, laboratory findings, histologic picture, and organs involved the two diseases are similar. The stools of patients with generalized sarcoidosis should be carefully searched for ova and parasites, and cutaneous tests should be made.

It has been known for many years that a granuloma is encountered as a manifestation of a hypersensitive state. Goddard [156] stressed this feature in 1947 when he used egg white as a sensitizing and shock antigen in guinea pigs. He found that formation of a granuloma was the specific reaction in the sensitized animal. Furthermore, he stressed the finding of plasmacytes but was not clear as to their role. It has been stressed in this paper that the association of sarcoidosis and other hyperergic states has been mentioned in the literature.[157] Case 2 described in this paper displayed the co-existence of necrotizing arteriolitis and sarcoidosis, while in Case 1 the disease was associated with rheumatic fever. That the presence of plasmacytes is a feature of sarcoidosis has been mentioned repeatedly in the literature and was a prominent feature in Cases 1 and 2 described in this paper. It is now believed that these cells are responsible for the formation of serum globulin.[158]

155. Freiman.[19] Nadel and Ackerman.[153]

156. Goddard, J. W.: Am. J. Path. **23**:943, 1947.

157. Teilum.[92] Staehelin.[149] Gartside.[150] Pullinger and Pirie.[151]

158. White, A., and Dougherty, T. F.: Endocrinology **36**:207, 1945.

It is suggested that sarcoidosis represents an altered capacity on the part of the host to react to various antigens. It is believed that nematode infestation may provide the necessary antigenic principles in some instances.

SUMMARY

A review of the available literature concerning the pathologic aspects of sarcoidosis has been presented. The greatest stress has been placed on the etiologic aspects and the pathogenesis of this disease. Two cases have been presented, and an attempt has been made to clarify the concept that generalized sarcoidosis must be differentiated from focal sarcoid lesions. Generalized sarcoidosis and nematode infestations are similar in epidemiology, laboratory findings, organs involved, and histologic reactions. It is believed that sarcoidosis results from an altered capacity of the host to react to various as yet unidentified antigenic substances, one of which may result from nematode infestation.

Case Reports

SUBLEUKEMIC PLASMA CELL LEUKEMIA

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THERE is a tendency in recent literature to regard plasma cell (or multiple) myeloma and plasmacytic leukemia as essentially similar processes representing only different stages of the same disease.[1]

These two conditions have basically certain similar features, such as multiplicity of lesions consisting of diffuse plasma cell infiltrations, progressive anemia, resistance to all known forms of therapy, and ultimately an unfavorable outcome.

In spite of these common characteristics, certain differential points separating the typical cases of plasma cell myeloma from those of plasmacytic leukemia seem to be apparent.

The subject is controversial and debatable, and the reported cases of plasmacytic leukemia are rather rare. For this reason the presentation of a case with a brief comment on its clinical and pathological aspects is made.

CLINICAL HISTORY

A white woman 45 years of age was admitted to the A. Barton Hepburn Hospital, Ogdensburg, N. Y., in November, 1950. Six weeks previously she had a "virus pneumonia" and then had experienced progressive weakness accompanied by occasional vaginal bleeding.

Physical examination on admission gave essentially negative results. Two days later her gums started to bleed and her spleen could be palpated 1½ fingerbreadths below the left costal margin.

The laboratory record was significant:

Blood red corpuscles	1,670,000/cu. mm.
Hemoglobin	4 gm. (25.2%)
Color index	0.78
Leucocytes	8,100/cu. mm.
Differential leucocyte count:	
polymorphonuclear neutrophiles, nonsegmented	7
segmented	55
lymphocytes	40
eosinophiles	1
Reticulocytes	1.6%
Thrombocytes	54,750/cu. mm.
Bleeding time	2 min. 54 sec.
Clotting time	5 min. 59 sec.
Blood nonprotein nitrogen	45 mg./100 cc.
Serum proteins (total)	6.9 gm./100 cc.
Albumin globulin ratio	2:1

From the Department of Pathology, A. Barton Hepburn Hospital.

1. (*a*) Bayrd, E. D., and Hall, B. E.: Unusual Remission After Radiophosphorus Therapy in a Case of "Acute Plasma Cell Leukemia," Blood **3**:1019-1024, 1949. (*b*) Meyer, L. M., and Rutzky, J.: An Unusual Case of Acute Plasma Cell Leukemia Treated with a Folic Acid Antagonist and Urethan, Cancer **4**:1043-1051, 1951. (*c*) Milliez, P.; Dreyfus, B., and Rathery, M.: Myélome ou cryptoleucose à plasmocytes: Caractères particuliers de la prolifération plasmocytaire, Bull. et. mém. Soc. méd. hôp. Paris **63**:860-865, 1947. (*d*) Rubinstein, M. A.: Multiple Myeloma as a Form of Leukemia, Blood **4**:1049-1067, 1949. (*e*) Stark, E., and Amidon, E. L.: Diffuse Plasma Cell Myelomatosis, Arch. Path. **46**:183-186 (Aug.) 1948.

A differential count on a sternal marrow smear gave percentages as follows:

Undifferentiated cells	60
Granulocytes	17.5
Erythroblasts	4
Lymphocytes	3
Megakaryocytes	0.5
Plasmacytes	5.0
Proplasmacytes	10.0

Plasma cell myeloma was suspected, but an x-ray survey of the skeletal system revealed no abnormalities; the urine did not show Bence Jones protein.

After several transfusions and administration of iron the patient's condition improved considerably and upon her request she was discharged on December 11. She remained at home under the care of her physician.

On December 18 she was readmitted to the hospital for further observation and treatment.

The laboratory record was as follows:

Red cells	3,000,000/cu. mm.
Hemoglobin	8.5 gm. (54%)
Color index	0.9
Leucocytes	4,900/cu. mm.
(The differential leucocyte count was not remarkable.)	
Blood nonprotein nitrogen	40 mg./100 cc.
Serum proteins (total)	6.7 gm./100 cc.

The patient was discharged on December 23.

On Jan. 2, 1951, she was readmitted with symptoms of respiratory distress. A right-sided hemothorax with collapse of the right lung was diagnosed by roentgenologic examination. Thoracentesis was performed, 2,100 cc. of dark bloody fluid being removed from the right pleural cavity. The laboratory findings at that time were as follows:

Red cells	3,400,000/cu. mm.
Hemoglobin	8.7 gm. (56%)
Color index	0.85
Leucocytes	3,300/cu. mm.

The significant cells found on differential leucocyte count were proplasmacytes, 2%, and atypical lymphocytes, 2%.

Bone marrow aspiration was contemplated, but the patient would not give consent. An x-ray examination was performed, but no structural changes of the skeletal system were demonstrable.

The patient's condition deteriorated steadily, and she died on Feb. 1, 1951.

The final diagnosis was not established, although plasma cell myeloma or some other form of cancer was suspected clinically.

AUTOPSY

The right pleural sac contained about 350 cc. of sanguineous fluid.

The right lung was partially collapsed and was airless and rubbery in consistency. On section there were areas of edema, congestion, and scattered hemorrhages.

The liver was enlarged (weighed, 2,650 gm.). Under the capsule and on surfaces made by sectioning there were numerous small, ill-defined grayish areas measuring up to 0.3 cm. in diameter.

The spleen weighed 840 gm. On the sectioned surface the parenchyma appeared distinctly congested, grayish red, and soft in consistency.

The left kidney weighed 210 gm.; the right, 200 gm. The capsules stripped readily, revealing smooth, pale surfaces. On section the parenchyma appeared swollen and edematous, but both cortex and medulla retained their usual markings.

The uterus revealed a cervical erosion of moderate size involving exo- and endo-cervix.

Several perihepatic and mesenteric lymph nodes were enlarged and firm in consistency. On cross section the surface was generally whitish and uniform, but here and there well-defined minute areas of necrosis were observed.

Bone marrow exposed in the middle shaft of the femur appeared deep red or slightly grayish. In addition, a few small, scattered grayish plaques, 0.2 to 0.3 cm. in diameter, were observed throughout the exposed area.

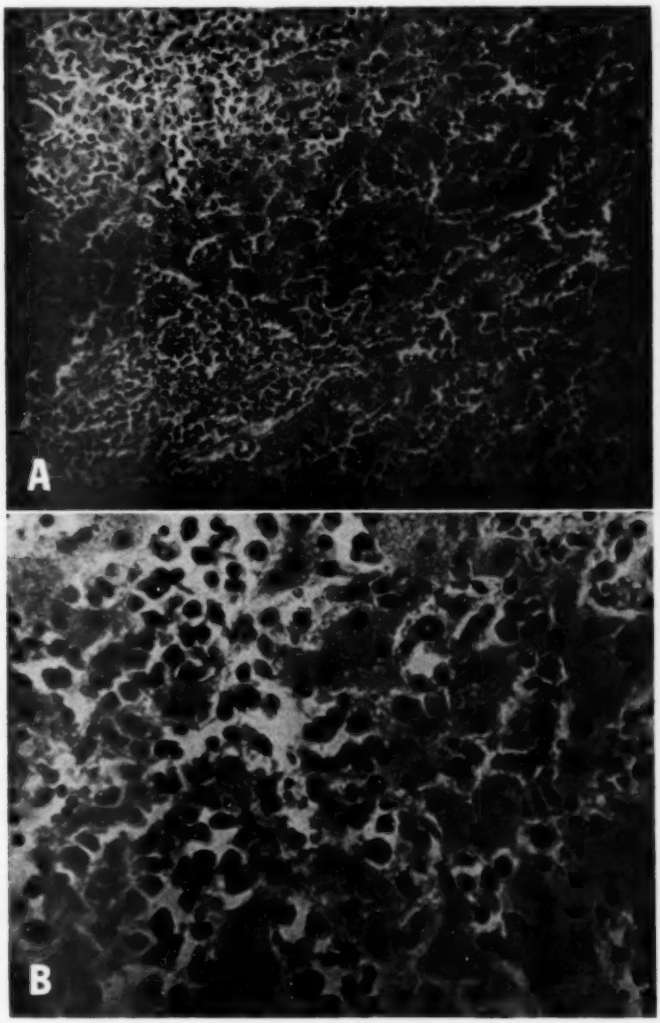

Fig. 1.—*A*, liver parenchyma diffusely infiltrated by plasma cells; hematoxylin-eosin stain; × 80.
B, liver sinusoids distended with plasma cells; hematoxylin-eosin stain; × 300.

MICROSCOPIC EXAMINATION

The bronchioles were hyperemic, edematous, and infiltrated with mononuclear cells. The alveolar spaces contained edema fluid and very little fibrin. Scattered

hemorrhages were noted throughout the sections. In the portion affected by atelectasis, the alveolar walls were in apposition in many areas.

In the liver the tissue spaces were diffusely infiltrated by plasma cells varying in degree of maturity. This was particularly impressive in the vicinity of the portal areas, where the accumulation of cells was extensive. By widespread fusion of such areas, a replacement of the liver parenchyma became prominent (Fig. 1*A*). The sinusoids were likewise distended with numerous plasma cells (Fig. 1*B*). The picture was one of diffuse infiltration rather than localized and well-defined metastasis.

The splenic parenchyma was diffusely infiltrated by numerous adult and younger forms of plasma cells. Occasional minute solid foci composed entirely of

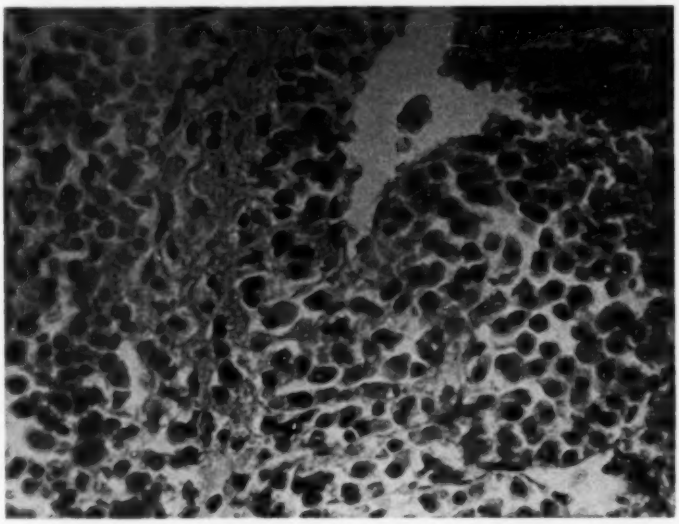

Fig. 2.—Spleen showing solid foci composed mainly of well-differentiated plasma cells; hematoxylin-eosin stain; × 300.

plasma cells were encountered (Fig. 2). The organ seemed to be severely congested, and the normal splenic structure was considerably blurred, as was indicated by a definite distortion of Malpighian bodies.

The kidneys revealed definite albuminous degenerative changes of the epithelium of convoluted tubules. In addition the interstitial tissues showed small foci of plasmacytic infiltration (Fig. 3*A*). These, however, were discretely scattered throughout the sections and bore no striking relation to any of the anatomical renal elements, such as glomeruli, tubules, or vessels.

The lymph nodes (perihepatic and mesenteric) were markedly infiltrated with plasma cells. Obliteration of the peripheral sinusoids, invasion of the capsule, and disappearance of the germinal centers were the striking features (Fig. 3*B*).

The normal bone marrow structures were replaced with plasmablasts, proplasmacytes, and plasmacytes, and there was little evidence of active red cell production (Fig. 4*A*). There was an estimated 88% of plasmacytes.

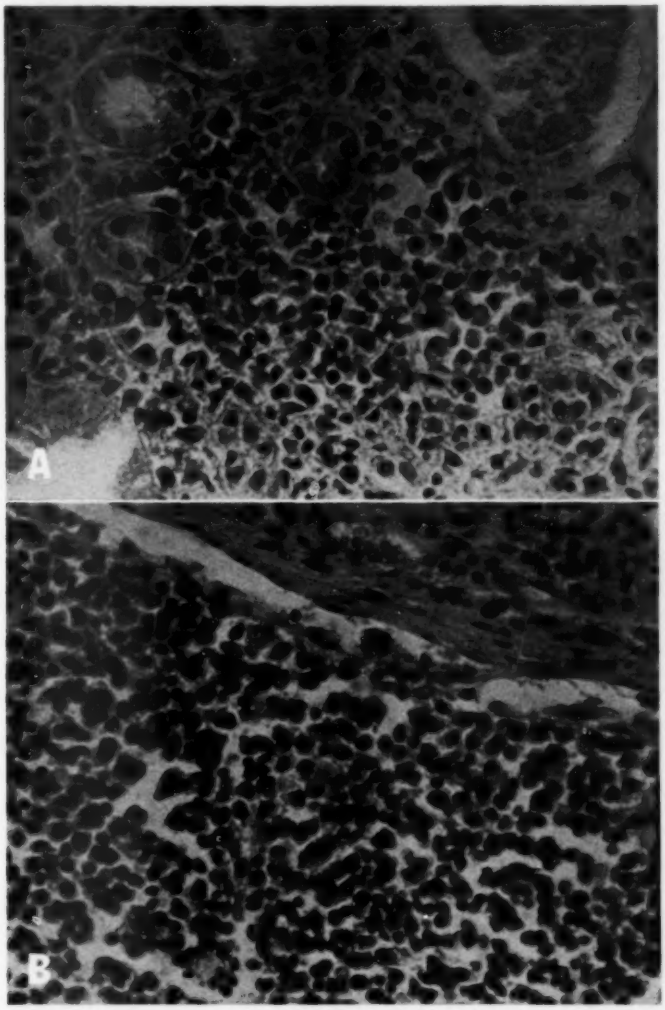

Fig. 3.—*A*, focus of plasmacytic infiltration in kidney; hematoxylin-eosin stain; × 300. *B*, plasmacytic infiltration of the lymph node periphery; hematoxylin-eosin stain; × 300.

The adrenal glands revealed scattered plasma cell infiltration of the periadrenal adipose tissue (Fig. 4*B*).

The eroded area of the uterine cervix revealed masses of cells, predominantly plasmacytes, infiltrating the base of the erosion. The picture was somewhat obscured by a superimposed inflammatory reaction.

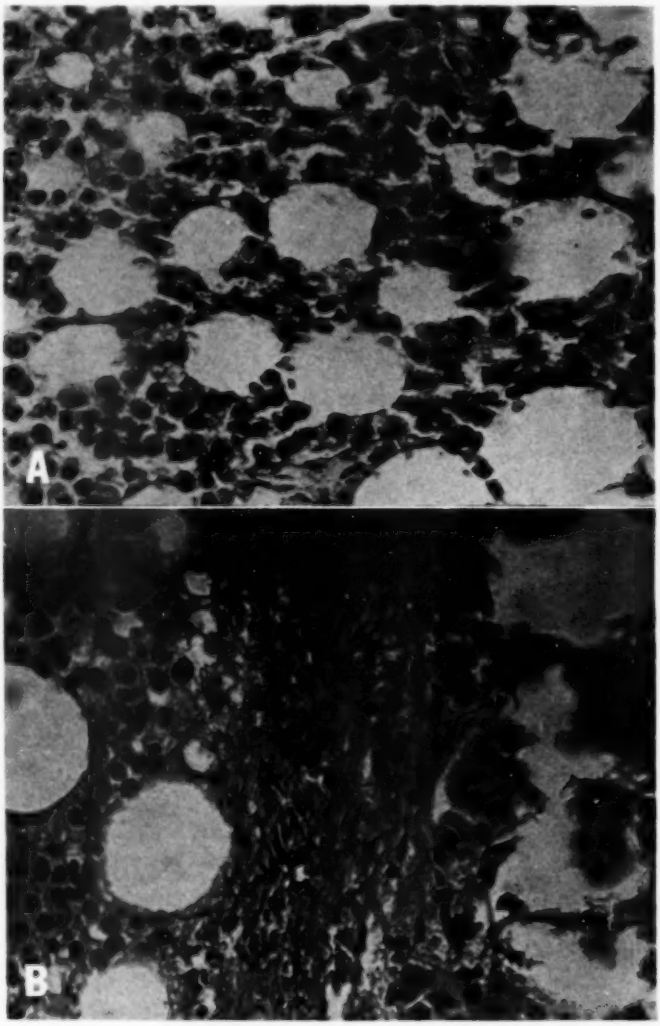

Fig. 4.—*A*, extensive plasmacytic infiltration of bone marrow; hematoxylin-eosin stain; × 300.

B, small focus of plasmacytic cells in periadrenal adipose tissue; hematoxylin-eosin stain; × 300.

COMMENT

In the case presented, the clinical diagnosis was not definitely established. The result of the x-ray skeletal survey was essentially negative.

A few plasmacytes found on one occasion in blood and increased numbers of cells found in aspirated marrow were not sufficiently significant to establish the diagnosis of plasma cell myeloma or subleukemic or aleukemic plasma cell leukemia.

Plasma cells may be observed in the blood and excess of plasma cells in the marrow in a number of other conditions.[2] The preponderance of undifferentiated and immature cells in the marrow studied further confuses the examiner and makes accurate diagnosis more difficult.[3]

The gross and the microscopic findings at necropsy were helpful in establishing the final diagnosis.

The case seems to conform with criteria established for subleukemic plasma cell leukemia. The diagnosis was based on (1) the profound anemia with thrombocytopenia; (2) the hemorrhagic episodes; (3) the short duration [1c]; (4) the diffuse leukemic plasma cell infiltration of marrow, liver, spleen, lymph nodes, kidneys, periadrenal tissues, and eroded cervical tissue; (5) the normal leukocyte count [2b] and the lack of constant and appreciable numbers of plasma cells in the blood, which was good evidence that the condition was subleukemic; (6) the hepatosplenomegaly.

The following observations were against the possible diagnosis of plasma cell myeloma: (1) the failure of repeated x-ray surveys of the patient's skeletal system and a detailed autopsy to disclose any bone lesion or real tumefaction anywhere in the body; (2) the normal serum protein levels.

Rubinstein [1d] stressed that bone involvement and hyperproteinemia are rather uncommon features in plasmacytic leukemia but common and significant in plasma cell myeloma.

It seems convenient to rely on these two characteristics in making a differential diagnosis between plasmacytic leukemia and plasma cell myeloma. Cases regarded as plasmacytic leukemia and showing hyperproteinemia and any evidence of bone involvement should be viewed with suspicion, perhaps, and would better be classified with the plasma cell myeloma group.

The concept that plasma cell myeloma is merely a variant or a different phase of plasmacytic leukemia is in reality difficult to prove. Present knowledge does not seem to be exact about the origin and the pathogenic properties of so-called plasma cells, and why their behavior differs on various occasions is not known. They are found in inflammations and in neoplastic conditions. In some cases of the latter, plasma cells have a tendency to exhibit an osteolytic action and/or to enter the blood. In other cases plasma cells, although morphologically identical, restrict themselves (as it is observed in this case) to an infiltration of the soft visceral tissues. Similar relations can be observed between lymphocytic leukemia and lymphosarcoma, where cells of the lymphoid series show essentially different pathogenic features in each of these conditions.

2. (*a*) Bayrd, E. D.: The Bone Marrow on Sternal Aspiration in Multiple Myeloma, Blood **3**:987-1018, 1949. (*b*) Lumb, G., and Prossor, T. M.: Plasma Cell Tumors, J. Bone & Joint Surg. **30B**:124-152, 1948.

3. Milliez and others.[1c] Lumb and Prossor.[2b] Bayrd.[2a]

Another example suggesting that plasma cells may represent pathogenetically different varieties are so-called solitary plasma cell tumors. These lesions are locally destructive but are without tendency toward generalization; in spite of the fact that they commonly involve bone or soft tissues, they seem to be unrelated to plasma cell myeloma or plasmacytic leukemia, and their prognosis is always favorable.[4] Unfortunately, they cannot be distinguished histologically from the true plasma cell myeloma, and a long period of observation is required before the accurate diagnosis of a solitary plasmacytoma can be established.[5]

The truth of the remarks of Moss and Ackerman [6] that the promptness with which plasma cell myelomas force their plasma cells into the blood stream and the amount of such cells should be a measure of the malignancy could not be demonstrated in this case. The patient's health was deteriorating rather quickly in spite of the fact that plasma cells were found in the blood in insignificant number and only on one occasion.

Bayrd and Hall [18] reported encouraging results in one case of acute plasmacytic leukemia treated with radioactive phosphorus. Similar attempts in cases of plasma cell myeloma were constantly disappointing.

SUMMARY

A case of subleukemic plasma cell leukemia is presented. It demonstrates the difficulty of establishing the correct clinical diagnosis and also points out that in spite of a certain similarity with plasma cell myeloma the plasmacytic leukemia (subleukemic form as well) seems to be an entity which in some cases presents clear and distinctive features.

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4. Christopherson, W. M., and Miller, A. J.: A Re-Evaluation of Solitary Plasma Cell Myeloma of Bone, Cancer **3**:240-252, 1950.

5. Chesterman, J. T.: Solitary Plasmocytoma of the Long Bones, Brit. J. Surg. **35**:440, 1948. Christopherson.[4] Lawrence, S. H., and Fortner, H. C.: Acute Plasma-Cell Leukemia Without Localized Bone Lesions, A. M. A. Arch. Path. **52**:384-389, 1951.

6. Moss, W. T., and Ackerman, L. V.: Plasma Cell Leukemia, Blood **1**:396-406, 1946.

News and Comment

Meetings.—The International Association of Medical Museums, American-Canadian Section, held its 41st annual meeting at the Hotel New Yorker, on April 9, preceding the meetings of the American Association of Pathologists and Bacteriologists. The afternoon program consisted of presentations and discussions on the "Technical Aspects of Radiobiology." Of special interest were some 25 scientific exhibits. The newly elected officers of the Association of Pathologists and Bacteriologists are James B. McNaught, M.D., president; Harold L. Stewart, M.D., vice-president; F. K. Mostofi, M.D., secretary-treasurer; Harold Gordon, M.D., Howard C. Hopps, M.D., and William O. Russell, M.D., incoming councillors. A total of 66 new members were elected. The next meeting of the Association is to be held April 1, 1953, at the Hotel Jefferson, St. Louis.

At the meeting of the Histochemical Society in New York on April 7-8, 1952, the following officers were elected: Dr. Stuart Mudd, University of Pennsylvania, president; Dr. J. Walter Wilson, Brown University, vice-president; Dr. Edward W. Dempsey, Washington University, treasurer; Dr. Ralph D. Lillie, National Institute of Health, secretary. The following councillors were elected for four years: Dr. Arnold Lazarow, Western Reserve University; Dr. Albert H. Coons, Harvard University. At the same meeting 62 new members were elected by the Council, and the Society elected R. R. Bensley and L. Lison to honorary membership. The next meeting will be held in Chicago, April 5-6, 1953.

Books

PATHOLOGICAL HISTOLOGY. By Robertson F. Ogilvie, M.D., D.Sc., F.R.C.P.Ed., F.R.S.E., senior lecturer in pathology and assistant in forensic medicine, University of Edinburgh; senior pathologist, Royal Infirmary, Edinburgh. Ed. 4. Pp. 506, with 295 figures. Price $8. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1951.

This edition includes a number of additions pertaining to the cardiovascular, respiratory, alimentary, urinary, reproductive, hemopoietic, nervous, and integumentary systems. The subject is more or less divided into general and systemic pathology. Because of this, it cannot be helped that the student, if interested in one subject, has to refer to several chapters on widely separated pages to obtain the information he seeks. Thus, carcinoma of the corpus uteri is discussed on page 323, while choriocarcinoma of the uterus is depicted and discussed on pages 152-159. Though not called an "atlas," the book contains 295 color photomicrographs which are of excellent quality. A very valuable item is the short description of the gross appearance of organ and disease included before the histologic details are discussed.

The book is clearly written, concise, and to the point. It constitutes an excellent help to the beginner in pathology and an important supplement to any relevant textbook. It can be recommended unhesitatingly.

ATLAS DER PATHOLOGISCHEN ANATOMIE. By Prof. Dr. Robert Rössle, emer. ord. Professor und ehemaliger Direktor des Pathologischen Instituts der Universität Berlin am Charite-Krankenhaus, and Prof. Dr. Kurt Apitz, weiland ao. Professor und Prosektor der Charité-Krankenhauses. Pp. 298, with 564 illustrations. Price 87 German marks. Georg Thieme, Diemershaldenstrasse 47, (14a) Stuttgart O.; agents for U. S. A.: Grune & Stratton, Inc.

The subtitle of this volume reads: "A collection of typical pictures of diseases of human organs." This is just what the atlas brings, with all the advantages and the few disadvantages inherent in such an undertaking. The volume may rightly be called a "picture book of gross morbid anatomy." The subject is divided into the conventional chapters of pathology, and

a short discussion of the pathogenesis of the lesions is presented in connection with the description of the disease, rather than of the depicted specimen. Only photographs of gross specimens are given.

Most of the pictures are colored, only a very few being black and white illustrations. They are of a superb quality rarely encountered in medical atlases. However, highlights are somewhat disturbing. Since a number of pictures show no highlights at all, one may ask if it would not be possible in future editions to eliminate at least those which are disturbing. Why is it necessary to draw in blood vessels in the heart valve as in Figure 24? This reduces the value of the picture to a mere schematic drawing. The basic inherent fault of this atlas, as of any other, is that it gives just one phase of a disease which often has continuous morphologic changes. Here, only typical changes are pictured. Thus, the beginner, for whom such an atlas is primarily designed, might not diagnose a specimen, because it just does not conform exactly to "the picture in the book."

Clinicians who have been away from this field will enjoy combing through the book, which may very well kindle the spark of the remnants of their knowledge of pathology. Pathologists will enjoy studying the pictures and accompanying notes and are bound to benefit by them. Taken in general, this volume represents a tremendous task executed in superb manner during trying times. Paper, print, and make-up are a fitting frame for this monumental work.

UROLOGICAL PATHOLOGY. By Peter A. Herbut, M.D., professor of pathology, Jefferson Medical College, and director of clinical laboratories, Jefferson Medical College Hospital, Philadelphia. Volumes I and II. Complete index in both volumes. Pp. 1222, with 527 illustrations, two in color. Price $24. Lea & Febiger, 600 S. Washington Sq., Philadelphia 6, 1952.

"This work on Urological Pathology is intended for the general practitioner, the medical student, the general surgeon, the gynecologist, and the urologist." The author did not specifically include the pathologist, but he might have done so.

After a short chapter on embryology, the work takes up in systematic fashion the following topics: urethra, bladder, ureters and pelves, kidneys, adrenals, and the male genital system (penis, prostate, seminal vesicles, spermatic cord, epididymes, testes, and scrotum).

The concepts underlying the book are praiseworthy. With the rapid progress in science there is indeed a great need for monographic treatment of system pathology, which will be useful to all students of disease who are at all concerned with that particular system. The present work is performed with great scholarship, with careful attention to details, frequently with encyclopedic coverage. There are very abundant illustrations, most of which are excellent, and very adequate bibliographies.

There are, however, some serious drawbacks. There is a rigid adherence to a detailed format of presentation. Thus, every condition is taken up under the following headings: definition, distribution, cause, clinical manifestations, gross appearance, microscopic appearance, complications, diagnosis, treatment, and prognosis. In the opinion of this reviewer, such a presentation is attempting to force pathology upon a Procrustean bed. Some conditions lend themselves easily to such a format. With others, especially the rare diseases, such a presentation appears stilted and unnecessary, wasteful of space and time.

The embryological discussions are rather weak and admittedly derivative. To one who does not already know the embryology of the urogenital system, the present treatment will not be instructive. Then, matters of clinical manifestation and treatment are outside the competence of the pathologist and in this work are also obviously derivative. There is, in brief, too great a dilution of Dr. Herbut's own contributions. His own studies of pathology are mingled with too much material which can be more profitably consulted in clinical or embryological texts.

The book would be far more useful had it been published in one volume rather than two. By more judicious presentation of material, and with more rigid control of photographs, the two volumes could, we feel, have been reduced to one, with a correspondingly reduced price and wider circulation.

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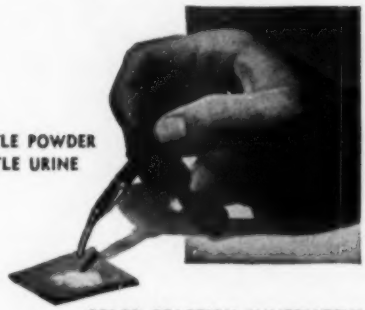

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